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THE PREVENTION OF INFERTILITY

A REPORT ON A PROPOSED METHOD TO PREVENT INFERTILITY: SELF-IDENTIFICATION OF RISK FOR INFERTILITY

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I. INTRODUCTION

There is a general impression that we are experiencing an "epidemic" of infertility in the United States. This impression is primarily based on increased public awareness of infertility. When people hear more about a problem (e.g. infertility) and it is discussed in books, magazines, radio and television, a general impression is formed that the problem has arisen recently or an acute increase has occurred. Perhaps the problem (infertility) has always been there and the only increase has been in public awareness. Whatever the cause of this increased awareness, infertility as a medical and social issue has moved from the background to the foreground. Intense medical and demographic interest is currently being focused on infertility.

The only available information that addresses the question of a perceived change in the prevalence of infertility comes from the National Surveys of Family Growth (NSFG), conducted by the National Center for Health Statistics in 1965, 1976 and 1982 (1,2). These surveys have identified some interesting trends and significant changes in the reproductive behavior of the U.S. population. The birth rate in the United States has declined since a post World War II peak in 1957; the birth rate has been below a replacement level for more than a decade. Therefore, the U.S. population is not in an uncontrolled expansion mode but, on the contrary, it is in a selective and shrinking mode. (With a relatively low birth rate there is a change in focus towards quality over quantity in terms of reproduction; infertility would tend to receive more attention in this

situation). Currently, the principle method of contraception is surgical sterilization and there has been a very significant increase in elective sterilization for birth control among both females and males. In 1982, twenty-five percent of couples between 15-44 years of age had undergone a sterilization operation; sixty-one percent of couples age 40-44 had been surgically sterilized. Women had an average of 2.6 children at the time they underwent sterilization, however, the NSFG indicated that 26% of sterilized women still desire another child (2). Although these women may never act on this desire, they number approximately two and one-half million women. This amounts to a potentially large request for reversal of sterilization in the future. Therefore, infertility exists even among a significant segment of the voluntarily sterilized population who are not considered in infertility statistics.

Further pertinent information from the NSFG surveys: In 1982, 8.5% of all currently married U.S. couples (with the wife 15-44 years of age) were infertile (1,2). If couples who have undergone surgical sterilization are excluded, this percentage becomes 14 percent. In terms of real numbers of people affected, between 2 and 3 million couples were found to be infertile in the 1982 survey. The three surveys enable us to determine whether there has been an increase in infertility over the 18 years studied. The only significant increase in infertility was found in the age group of women 20-24 years old. Women in this age group experienced an increase from 4 to 7 to 11 percent in these surveys. This 20-24 age group is important because one out of three births in the United States occurs to women of this age. The increased infertility in this age group

may be secondary to sexually transmitted diseases, because this problem was most prevalent in the women aged 15-19 in the 1976 survey. Except for this particular age group, a summary of the latest survey concludes that the proportion of the reproductive age population that is infertile has not changed dramatically since 1965 (1).

There are several interesting characteristics of the infertile population in the United States: There is a disproportionate number of black couples who are infertile; couples who have less than a high school education also experience more infertility. Overall, about 30 percent of infertile women had primary infertility and 70 percent had had at least one child (3). Compared to fertile women, those experiencing infertility were, on the average, four years older. Comparing fertile and infertile women, there was no difference in age at menarche nor age at first intercourse. However, infertile women had a significantly decreased prior use of contraception including intrauterine devices (3). These data are helpful in the design of a program to address the infertility problem. The more we understand about the infertile population, the better we can address the infertility problem.

The National Surveys of Family Growth have all found an expected increase in infertility with the age of the female partner. In 1982, 11 percent of the women aged 20-24 were infertile while 25 percent of the women in the 35-39 year bracket were infertile (1). The decline in female fertility with age is a real phenomenon when two lines of evidence are considered: 1) historical surveys of well defined populations have found a similar and

consistent decrease in fertility with age (4); 2) women exposed to a similar number of cycles of donor insemination have decreased success rate with increased age (5). Considering female age as an isolated factor, it is estimated that a woman aged 35-39 is 30% less fertile than when she was 20-24 (4). There is a sharp and well documented decline in female fertility after age 40. This decline in fertility with increased age becomes important, considering the recent trend in delayed childbearing which has become part of our modern society (6).

While there has been no recent pronounced increase in the prevalence of infertility in the United States, there has been increased use of medical services for infertility. In 1968 there were 600,000 visits to private physician offices for infertility services in the United States, these increased to 900,000 by 1980 (7). Apparently, an increased proportion of infertile couples are seeking health care to evaluate their condition. However, the NSFG survey indicates only 50 percent of women with primary infertility and 25 percent of women with secondary infertility ever seek care for their condition (3). Therefore, although office visits are on the rise for infertility, a majority of women never seek medical intervention for their problem. White women, women with higher socio-economic backgrounds, and women with more education were all more likely to seek infertility services (3). Considering the overall decline in obstetric patients accompanying the decrease in the birth rate and the increase in office visits for infertility, a higher percentage of

obstetric-gynecologic patients would be infertile. An increased use of infertility services is a helpful trend in terms of the anticipated response to any plan designed to address the infertility problem.

Part of the increased public awareness of infertility may be due to a number of social factors. Effective means of contraception has allowed couples to control their fertility in an efficient manner that was not available to older generations. This ability to control fertility and delay childbearing would give people an impression of overall control of their fertility. Therefore, when infertility occurs and it occurs in a condensed interval (delayed childbearing), there is heightened awareness of the problem and people are more likely to seek medical help than in the past. Another social factor that impacts on infertility is the relative unavailability of healthy newborn infants for adoption. Adoption was a rather easy alternative for infertile couples in previous generations, but this option is much less available to the current generation because of the relative scarcity of relinquished infants. Another possible reason for increased infertility awareness has been the publicity surrounding the new reproductive technologies, such as in vitro fertilization. Awareness of new therapies and the mistaken impression that medical science can now cure all infertility problems, has led to inflated expectations in many infertile couples. Another factor that may have impacted on infertility awareness is the increased availability of medical services for infertility. The medical community has increased the availability of infertility services in the last decade; this is exemplified by the membership of the American Fertility Society (3600 health care profes-

sionals in 1974; the membership is currently over 10,000). All of these factors have influenced and increased awareness of infertility by the public and the medical community.

Even if there has been no dramatic increase in the percentage of infertile couples, this medical problem has a widespread effect on our society. First of all, any medical problem that affects an estimated 2 to 4 million couples is a major problem simply in terms of sheer numbers. These numbers add up to a large cost which can be measured in several ways: dollars expended, time and energy spent by patients and physicians, human suffering, and inefficiency in terms of delayed life decisions by infertile couples. Fortunately, we live in a more enlightened age in that reproductive problems such as infertility are "out of the closet" and available for public discussion and debate. The medical knowledge in regards to the causes of infertility and the number of treatments available are all on the increase. However, medical therapy for infertility is expensive and is only moderately successful. Considering all these factors, this is the opportune time to address the infertility problem in this country. Considering the scope of the problem and the associated issues, by far the best way to address our infertility problem would be <u>prevention</u>.

In order to prevent any problem, it is most helpful to identify causal factors. Many causal or risk factors for infertility have been identified. While medical knowledge is incomplete (and will always be so), enough is currently known to design a prevention program. Furthermore,

many of the risk factors for infertility that have been identified are reversible to some degree. Even if a risk factor for infertility is irreversible (has already caused infertility), earlier identification would allow more time for medical intervention.

While prevention is clearly the optimal approach to infertility, any prevention plan should fulfill certain characteristics in order to be effective. A prevention plan should be simple and understandable in order for it to be applied to the general population. A plan should be cost effective in terms of saving more resources than it expends. An ideal prevention plan should respect individual privacy and would not disrupt individuals nor their relationships. It must be possible to measure the effect of any prevention plan in order to assess results.

With these attributes in mind, we have developed a specific plan to prevent infertility. This prevention plan is the subject of this report. The plan calls for people of reproductive age to administer a self-test to ascertain whether they have developed or acquired any risk factors for infertility. A person with one or more identified risk factors may already be infertile or could become infertile in the future. Persons identified to be at risk would be made aware of steps they should take to determine whether they are infertile and/or to decrease their risk of becoming infertile. The proposed plan relies upon a questionnaire to identify and educate potentially infertile people. A workshop was recently convened to discuss this plan under the auspices of the Office of Technology Assessment of the U.S. Congress and the Department of

Obstetrics and Gynecology at the University of Washington. This workshop was held in Seattle, Washington on June 19, 1987. The program for this workshop is contained in Appendix I and the participants are listed in Appendix II. The remainder of this report will discuss this specific plan to prevent infertility.

II. SELF IDENTIFICATION OF PERSONS AT RISK FOR INFERTILITY BY MEANS OF A QUESTIONNAIRE

A. The Target Population to Receive Questionnaire

Men and women of reproductive age will be the population for whom this questionnaire is intended. An age range of 18-35 would seem to be appropriate. [Men and women below age 18 tend to be less mature and not at all focused towards planning their reproductive future. Persons greater than age 35 have relatively little time left to conceive]. It is envisioned that the target population would not currently be attempting to conceive at the time they take the questionnaire. These men and women would either not be sexually active or would be currently using some form of contraception. Persons who are currently attempting to conceive would not be appropriate subjects for this questionnaire (even if they are infertile, their demonstrated lack of fertility would be an indication for a medical evaluation). That is, the questionnaire will be designed to identify individuals who may have a future infertility problem while direct medical testing of fertility potential should be reserved for couples who are infertile.

Even though it is couples who are infertile and not individuals, different questionnaires will be designed for male and female populations. Many of the risk factors for infertility are quite different between men and women; therefore, separate questionnaires

will be made for each sex. A number of settings have been proposed that would appear to be appropriate for exposure to the questionnaire. It would seem that people in these settings would be predisposed to fill out a questionnaire pertaining to their reproductive potential. Some examples of proposed settings are:

(1) Men entering military service.

(2) Women presenting to their private obstetrician/gynecologists for annual examinations.

(3) Women who attend Planned Parenthood and similar family planning clinics.

(4) College students (men and women) who consult the student health service.

(5) Patients (men and women) who are being seen in oncology clinics (at risk for loss of their fertility).

(6) People having well patient care (e.g., annual physicals under a prepaid health plan).

(7) People (men and women) attending sexually transmitted disease clinics.

These are examples wherein both relatively young people interface with the health care system. It is presumed that most persons in such settings would be inclined to find out more about their reproductive potential if given the opportunity through this questionnaire.

B. Specific Goals for the Prevention of Infertility Questionnaire

This proposed method to prevent infertility by using a questionnaire would seek to improve the reproductive health of the population in a number of ways. First, it is anticipated that exposure to the questionnaire would serve to educate people in regards to reproduction. The questions would identify potential reproductive problems of which a person may previously have been unaware; each question would also include a comment and recommended action in response to certain answers. Even if a person exposed to the questionnaire has no specific risk factors for infertility, they may learn from the questionnaire and share what they learn with their associates.

A second major benefit of the questionnaire approach would be the identification of people who are already infertile. An example would be a woman who has had several episodes of pelvic inflammatory disease and therefore has approximately a 75% chance of having obstructed fallopian tubes (8). Obviously, there is no preventative aspect to the identification of persons who have already acquired infertility. However, a beneficial effect would be anticipated if a person's infertility is identified sooner (e.g., at a younger age). A person's reproductive lifespan is finite; the sooner infertility is identified, the sooner appropriate therapy can be applied. The earlier the age at which the problem is recognized, the greater the number of options available to an infertile person.

A third goal for the questionnaire approach is the identification of persons who are currently at risk but have not yet become infertile. In this situation, prevention can be applied in the true sense of the word. There are a number of examples of behaviors or physical symptoms that can be identified by questionnaire that may impact a person's future fertility. Some examples would be: multiple sexual partners (both sexes); chronically underweight (female); painless but persistent scrotal swelling (male); pain with intercourse (female). If risk factors for infertility are identified at an early stage and appropriate measures are taken to decrease the risk, then fertility may be preserved. It is assumed that a significant number (perhaps a majority) of people with infertility risk factors will not have already acquired infertility.

A fourth anticipated benefit associated with the use of the infertility questionnaire would be the identification of non-reproductive disease processes. Certain diseases that affect a person's general health have signs and symptoms that appear in the reproductive system. An example for women would be the presence of galactorrhea (breast fluid) which can be a sign of a pituitary tumor; a male example would be a mass on the testicle which could be the sign of an early testicular cancer. Earlier identification and treatment of these non-reproductive diseases would clearly promote the general health of the population.

A fifth benefit that could result from use of the questionnaire is reduction in iatrogenic infertility. Infertility that is a direct result of prior medical care is considered to be iatrogenic (9). An example of iatrogenic infertility would be an unindicated oophorectomy or salpingectomy for benign disease. If a person's knowledge and awareness of their reproductive potential increases after exposure to the questionnaire, they should be better able to assess the implications of diagnostic and therapeutic recommendations by health care providers.

The overall goal of the questionnaire method to prevent infertility is a reduction in the prevalence of infertility in the reproductive age population and an increase in their knowledge concerning reproduction. Any reduction in infertility in the population at large would be very significant, even if the reduction amounted to only several percent of the infertile population. Considering the overall costs (time, money, health care resources, etc) of infertility, a real decrease via the use of a simple questionnaire would be a tremendous accomplishment.

C. Design of the Prevention of Infertility Questionnaire

The questionnaire itself would have to be an effective instrument in order for this plan to accomplish its goals. It is anticipated that separate questionnaires would need to be developed for men and women. These questionnaires would have to be designed in straightforward language, and in a clear manner so that they can be understood by people with varying educational backgrounds. Each questionnaire would

have a brief introductory statement which would describe its content and purpose. A brief closing statement would appear after the questions which would encourage the person to follow through with the recommended behaviors. The body of each questionnaire would contain a series of questions based on known risk factors for infertility. The back page would have a set of suggested behaviors that would correspond to the questions on the front page. That is, a person would answer the questions on the face sheet and thereby transpose marks onto the back sheet that would suggest appropriate behavior for any risk factors identified. The mark on the back sheet would indicate the suggested behavior to identify or reduce infertility. The person filling out the questionnaire would receive an immediate response when handed the back page at the time they turn in the questionnaire. This prevention system would need to make available counselors and/or educational material for persons who have identified themselves as potentially infertile. The purpose of the counseling-information system would be to educate, decrease anxiety, and encourage appropriate responses.

During the validation phase of the questionnaire (and perhaps afterwards as well) it would be necessary, for follow-up purposes, to identify each individual who fills out a questionnaire. This could be accomplished by attaching a half page identifying information sheet to the front of the questionnaire. The identification sheet would be matched to each questionnaire by a paired number. In this manner a given set of responses could be matched to a given individual and

thereby facilitate follow-up. The impact of the questionnaire on a person's knowledge, behavior, and reproductive outcome could then be determined at a later date.

D. Development of Specific Questions for the Questionnaire

The development of specific questions that would serve a multi-faceted purpose (education; identification of risk factors) would be a key element to the success or failure of this approach. The questions would need to be clear, simple, and relevant. In order to develop appropriate questions, several guidelines would have to be kept in mind:

(1) The questions would need to cover most of the known major risks for infertility for both men and women respectively.

(2) The questions should concentrate on the major causes of infertility.

(3) The questions should concentrate on infertility risks that can be comprehended and/or recognized by a lay person. For instance, a man can understand and recognize whether one testicle is smaller than another and, likewise, a woman can recognize whether she is underweight. However, it would be difficult for a lay person to recognize what is significant "stress" in their life.

(4) Selection of questions should also consider the potential for the health care system to verify whether a problem exists if an infertility risk factor is identified. For example, the verification of tubal obstruction is simpler than the diagnosis of luteal phase deficiency in current medical practice.

(5) A final item that needs to be considered is the potential reversibility of reproductive health problems that may be detected by use of the self assessment questionnaire. For instance, anovulation and amenorrhea that is present after voluntary weight loss is quite reversible while anovulation secondary to prior chemotherapy is relatively irreversible.

Sample questions were submitted by the participants in the recent workshop on the prevention of infertility in Seattle. These physicians and scientists submitted over 100 questions, in rough draft form, to facilitate discussion of infertility prevention by the questionnaire method. Each question was accompanied by a suggested behavior in keeping with the specific format for this questionnaire. Appendix III contains a series of questions selected from those submitted at the workshop. A wide spectrum of infertility risk factors were addressed. The number of questions submitted made it clear that a sufficient number of probable risk factors were known to produce a meaningful questionnaire. The questions in Appendix III are acknowledged to only be in rough draft form and would require extensive refinement. It is important to also recognize that this one day workshop probably did not, identify all suspected risk factors for infertility.

E. Precedent for the Questionnaire Method to Self-Identify Individual with a Potential Reproductive Problem

At the recent workshop on prevention of infertility, a participant brought to the attention of the group the fact that an obstetric questionnaire had been developed and was in use in North Carolina. Dr. Robert Cefalo and his associates in the Department of Obstetrics and Gynecology at the University of North Carolina developed a preconceptional questionnaire that addresses specific risk factors in perinatal medicine (10). Dr. Cefalo was contacted and graciously provided information about their preconceptional health appraisal questionnaire. Their program of administering the preconceptional questionnaire recently began in the state of North Carolina. The current target population is 15 health department family planning clinics that are located in different parts of the state. A preliminary report is available involving 1,761 family planning patients who completed appraisals between July and November, 1986. There are 53 items on their questionnaire and the average patient had seven preconceptional risk factors (13%). A large majority of the patients indicated that the questionnaire was easy to understand, most of the women were interested in the information and the majority indicated that they had learned new things. The initial experience in North Carolina with the preconceptional questionnaire has been highly favorable. Appendix IV is a copy of the preconceptional health appraisal currently in use in North Carolina.

F. Response of the Health Care System to the Questionnaire Plan

The self-identification of infertility by questionnaire will identify men and women who may have a problem that could render them infertile. Each positive identification of a risk factor will be accompanied by a suggested action or behavior change. The suggestions will generally include one or both of the following:

(1) An explanation that a certain behavior increases risk and a suggestion to change that behavior.

(2) Consult a physician

For most of the risk factors that would be addressed in the questionnaire, there is a medical test that will identify whether the risk factor has caused damage to the reproductive system in a given individual.

It is expected when an individual consults their physician, that the doctor will obtain a further history and order appropriate tests if that approach seems prudent for that patient. Some examples of tests would be:

(1) A hysterosalpingogram to determine whether a woman has tubal obstruction.

(2) A semen analysis to determine whether a man has impaired spermatogenesis.

(3) A basal body temperature chart to determine whether a woman is ovulatory.

While the questionnaire will only touch on a given subject or risk factor, it is expected that a physician will obtain more information and delve further into the potential problem. However, it must be recognized that there can be risks associated with infertility tests. The risk of investigating someone for infertility can be as minimal as time and monetary expense or it can present a real medical risk such as acute pelvic inflammatory disease following a hysterosalpingogram. An assumption of the questionnaire approach to preventing infertility is that it is beneficial to identify whether a risk factor has damaged the reproductive system of an individual prior to that person actually attempting to conceive. This assumption is based on the consideration that each person has a limited reproductive lifespan, and earlier identification would allow earlier intervention and/or selection of alternatives. This method further assumes that physicians in practice will generally agree that it is prudent to investigate a person's fertility prior to a couple becoming infertile by a year of unprotected intercourse without conception.

While the questionnaire plan presumes individual physicians will evaluate each person's risk on an individual basis and proceed to preform appropriate tests, there is the potential for inappropriate responses by the health care system. The health care system could over or under respond to a patient who presents with possible infertility as identified by the questionnaire. An inappropriate response would be indifference and unwillingness to perform any tests to determine the presence or absence of infertility. An excessive

response could occur in terms of either diagnosis or therapy. An example of excessive diagnostic intervention would be the use of laparoscopy to diagnose tubal disease when a hysterosalpingogram could be used for the same purpose. In general it would be excessive to apply infertility therapy to people who are not proven to be infertile. The recommended response to identification of reproductive system damage would generally be encouragement to attempt conception as soon as individual circumstances would allow. Examples of inappropriate therapeutic interventions would be: treatment of a man with a borderline low sperm count without first having him test his fertility. An example of inappropriate timing of therapy would be the performance of a salpingoplasty operation on a woman who is not planning to attempt conception for several years after the procedure. It is known that most pregnancies occur in the first 1-2 years after tubal surgery and this favorable interval would be lost if surgical intervention was not properly timed. Considering there is a potential for inappropriate responses by the health care system, it is probable that such responses will occur. However, it is expected that such responses would only occur in a small minority of cases identified by the questionnaire plan. An attempt to both monitor and prevent inappropriate responses would be part of the system. The questionnaire plan will incorporate a local medical director, knowledgable in reproductive medicine, in each locale where the plan is applied. The medical director would be available for consultation and thereby would help insure that the health care system responded in an appropriate manner.

F. Potential Problems that Could be Associated with Prevention of Infertility Questionnaire

It must be recognized that the use of the prevention of infertility questionnaire has the potential for a negative as well as positive impact. One potential problem has already been discussed; the occurrence of inappropriate responses by the health care system. Another potential negative effect of the questionnaire is instilling alarm or anxiety in persons who have identified themselves as being at risk for infertility. To some extent, induction of anxiety cannot be avoided and can be helpful in the sense that anxiety becomes the force that moves people to follow through with the suggested behavior regarding their fertility. However, excessive anxiety about one's potential infertility could lead to inappropriate behavior by some individuals. It is not necessary to tax one's imagination to think of some examples of individual behavior that would be counterproductive. An example of negative behavior for men: a man who becomes alarmed because the questionnaire indicates he may be infertile and deliberately attempts to prove his fertility outside of a significant relationship. Examples of some negative behavior for women: a woman who becomes married sooner or marries someone she otherwise would not pick as a mate because she is anxious about her fertility; deliberate attempts at achieving pregnancy by a single woman out of fear of not being able to get pregnant in the future; a woman keeps an otherwise unwanted pregnancy out of fear of not being able to become pregnant again.

This questionnaire could create feelings of guilt in people who identify themselves as potentially infertile if certain activities in their past are the probable cause of this possible infertility. (Regret in regards to previous activity that may have caused infertility would be an appropriate response while guilt per se would be an unhealthy response). There is another negative individual response that could occur in a segment of the population after exposure to the questionnaire - apathy. Whereas some individuals may feel guilty and anxious after being exposed to the questionnaire, others may be apathetic and not care enough to change their behavior or follow through with the recommendations. Considering that people are quite variable in their responses, it would be naive to anticipate there would not be some extreme responses at both ends of the spectrum. However, it is expected that excessive anxiety or apathy will be the response of only a small segment of the population exposed to the questionnaire.

Another potential problem area with the self-identification questionnaire again concerns the health care system. The use of the questionnaire is expected to create a need for medical services from the health care system for those identified as potentially infertile. Not everyone in our society has equal access to the health care system. The main obstacle to access is inability to pay for medical services. Health care services for the poor tend to de-emphasize infertility as a priority. Therefore, some people may have the desire but not the ability to follow through with this plan. Another

possible problem that could develop with use of the questionnaire is excessive demand and/or response by the health care system in terms of medical resources expended. Considering the data from the recent National Survey of Family Growth, only 25-50% of infertile women seek medical care for their infertility (3). An impact of the questionnaire could be increased demand for infertility diagnosis and treatment with the end result a greater expenditure of health care resources.

It is well to recognize potential problems with any new proposal in order that these concerns can be anticipated, recognized, and prevented where possible. The potential problems mentioned can be prevented and/or minimized to a large degree, by the proposed support system to accompany use of the questionnaire. This support system is discussed in the next section. Moreover, it is important to consider this proposal in terms of overall benefits and risks. Despite the recognized potential for problems (risks) as discussed in this section, the anticipated overall benefit in terms of improved reproductive health would far outweigh any negative aspects.

H. Implementation of this Prevention of Infertility by Questionnaire Plan

The implementation of this proposal would consist of several steps: The basic steps would be: 1) Questionnaire development. 2) Selection of target populations for the pilot test. 3) Develop a protocol for promotion, distribution and use of the questionnaire. 4) Follow up persons who were exposed to the questionnaire and assess any effect.

5) Decide whether the program had achieved its goals and whether it had an overall beneficial effect. 6) If the overall assessment is positive, then move forward with a wider distribution of this program.

The development of a useful questionnaire would require considerable thought and careful consideration of potential questions and suggested behaviors. The rough draft of potential questions contained in Appendix III serves both to illustrate potential questions and the refinement thereof that would be necessary. It is anticipated that a committee would be formed to develop the questionnaire. Most of the committee members would be subspecialty physicians in reproductive medicine who would develop and refine a questionnaire. These committee members would combine their own clinical experience with their knowledge of the medical literature to produce clear and relevant questions. The suggested behavior for each question would need to be discussed and a consensus developed. Other important members of the questionnaire development committee would be: educators with expertise in developing questions and tests; public health professionals and epidemiologists with their perspective on medical issues in relation to populations.

The second phase would be the identification of target populations in specific geographic sites. Several target populations would appear to be appropriate for initial trials of the questionnaire. Examples would be: (1) Military recruits. (2) Women attending Planned Parenthood clinics. (3) Women consulting private

obstetricians/gynecologists. The geographic sites would consist of cities or locales spread throughout the United States. It is estimated that six to twelve separate sites would be selected for a trial of this plan. The sites would be selected based on geographical location as well as local interest and available expertise.

The third phase of implementation would be the promotion, distribution and use of the questionnaire. It is envisioned that a team would need to be formed in each participating region or city. It is estimated that each team would consist of a full time coordinator, a part time medical director and part time counselors. The coordinator would work in the health care setting with the selected population and pertinent health care professionals (e.g., physicians, nurses). Among the coordinator's responsibilities would be: development and maintenance of interest in the program; overseeing the operation; and making certain that relevant data was being collected. It is expected that each geographic site would also have a medical director, knowledgeable in reproductive medicine, who would both serve as a medical consultant and supervise the activity of the coordinator. The counselors would be appropriate personnel (e.g., nurses) at each specific site where persons would be exposed to the questionnaire. A counselor would receive each questionnaire, look over the responses, provide further information when necessary, encourage compliance, and be alert for inappropriate responses. A national coordinator and a national medical director would be necessary to oversee and coordinate the activities of the various geographic sites.

The fourth phase would be follow-up and analysis. A system would be developed for identifying and contacting persons who participated in the project. For instance, each person could fill out an identification sheet that could be matched to their questionnaire. Both individual and questionnaire data would be entered into a central computer to facilitate data analysis. Persons would be followed up in terms of their reaction to the questionnaire, amount of knolwedge gained, and any changes in their behavior. It would be difficult to ascertain any changes in reproductive outcome (e.g. ability to conceive) considering the relatively short duration of the pilot test. In order to reliably assess the effect of this plan, it would be necessary during the trial period to have a matched control group who were not exposed to the questionnaire. A control group could be developed by distributing the questionnaire to the target population only on even numbered days and only identify control persons on odd-numbered days. The participants and controls would have to be matched for such characteristics as age, sex, race, socio-economic status, and educational background. It is estimated that the trial period would take 1-3 years with another year required to compile and analyze the data.

The decision to proceed with expanded implementation of this infertility questionnaire plan would be based on an overall assessment after the trial period. The assessment should be based on: 1) Appraisal of the system by individuals who participated. 2) The demonstration of positive changes in reproductive behavior or health.

3) The costs that were experienced during the trial. 4) Analysis of any problems that developed. 5) An overall assessment whether the prevalence of infertility would likely be reduced by this method.

If the overall assessment of this questionnaire method is favorable, then the final step would be for implementation on a wider scale. It is anticipated that modifications in the questionnaire and its use would be forthcoming from the experience gained in the trial period. An estimated timeline for the implementation process is contained in Appendix V.

III. SUMMARY

There has been an increase in public awareness of infertility. However, it does not appear that infertility rates have increased signficantly during the last two decades. Nevertheless, along with the declining birth rate, infertility is a major medical and social problem in the United States. The cost of infertility, considering expenditures of time, energy and health care resources, is substantial. Even if the cost of infertility treatment was ignored, the traditional medical approach to the treatment of infertility is flawed in the sense that it is only effective in perhaps half of the couples affected. Therefore, prevention is a very attractive approach to the infertility problem and an efficacious prevention plan would improve the reproductive health of the U.S. population. The causes of infertility have been identified to the extent that there are multiple probable risk factors for most types of male and female infertility. Identification of probable causality and suspected risk factors makes prevention a feasible approach. Much infertility can be attributed to the lifestyle and habits of the persons affected. In other words, much infertility is acquired by individuals who choose or have chosen behavior that is detrimental to their reproductive health. In this context, infertility is preventable.

A prevention plan for infertility based on a self-identification questionnaire has been presented in this report. The questionnaire would identify young men and women (not currently attempting to conceive) who may already be infertile or are at risk to become infertile. There is an

expectation that increased knowledge regarding risk of infertility will cause a person to protect their reproductive health or seek infertility treatment at an earlier age.

The proposed plan appears to be feasible. Effectiveness is anticipated in terms of educating the population and possibly changing behavior to prevent infertility. While it would be best to proceed with this prevention of infertility method now, there are no plans for implementation at this time. This prevention of infertility plan awaits sponsorship. Considering the estimate of 4-5 years for implementation on a large scale, a favorable response to this proposal is necessary in the near future.

APPENDIX I

Office of Technology Assessment
Congress of the United States

University of Washington
Department of OB/GYN

PREVENTION OF INFERTILITY SYMPOSIUM

Westin Hotel
Seattle, Washington
Friday, June 19, 1987

PROGRAM

8:00	Continental Breakfast	
8:30	Welcome-Outline Agenda	Michael R. Soules, M.D.
8:35	Perspective of Office of Technology Assessment	Gary Ellis, Ph.D.
8:45	Epidemiology of Infertility - Summary of Recent Studies from King County	Beth Mueller, Ph.D.
9:30	Iatrogenic Infertility	William Keye, M.D.
10:00	Coffee Break	
10:15	Prevention of Infertility - The Idea of Self-Identification via a Questionnaire	Michael R. Soules, M.D.
10:45	Small Working Groups (Pairs) Group A - Seattle Room Group B - Board Room	
12:00	LUNCH	
2:00	Questionnaire Design	All Participants
3:00	Implementation	All Participants
4:00	Adjourn	

APPENDIX II
PREVENTION OF INFERTILITY SYMPOSIUM

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APPENDIX III

Questions - Recommended Behavior
Selected from questions submitted at Prevention of Infertility Workshop, June 19, 1987

Male

Question:
Do you feel that having children is very important to your goals in life?
Behavior:
You should develop five and ten year life plans that will include the opportunity to conceive and have children.

Question:
Have you considered the role of children in your marriage and come to an understanding regarding number of children and when you will have children?
Behavior:
If you are involved in a significant relationship, you should initiate discussion on these issues.

Question:
Have you had unprotected intercourse for over one year without your partner becoming pregnant?
Behavior:
You may be at increased risk for infertility.

Question:
True (yes) or false (no), a woman is only fertile on day a month?
Behavior:
If you answered no, you may have a misunderstanding about the relationship between the timing of sex and pregnancy. Consult your physician, who will clarify this relationship.

Question:
Have both of your testes been in your scrotal sac since birth? If not, did you have surgery or hormonal treatment?
Behavior:
Consult your physician

Question:
Are you experiencing, or have you experienced frequency of urinating, a discharge or burning on urination?
Behavior:
You may have an infection that could affect your future fertility, and that of those women you had sex with. See your physician and tell your sex partner(s) to see one also.

Question:
Is one of your testicles significantly larger than the other?
Behavior:
You could have a low sperm count. Consult your physician.

Question:
Have you ever had a lump in the groin, significant pain of the testes or scrotum?
Behavior:
This lump or pain may indicate that you may have problems producing sperm. Consult your physician.

Question:
Have you ever noticed an extra fullness or pressure in the scrotum or been told that you have varicose veins in the scrotum?
Behavior:
You could have a varicocele or varicose veins in the scrotum. Consult your physician, who may perform a careful examination of the scrotum and semen analysis and sperm count.

Question:
Do you use alcohol, cigarettes, marijuana, cocaine or prescription drugs?
Behavior:
Use of these products may reduce your fertility. Consult your physician regarding their potential effects on your fertility.

Question:
Have you ever had exposure to radiation, chemotherapy, pesticides, diethylstilbesterol (DES, when your mocher was pregnant carrying you), or other chemicals?
Behavior:
You could have decreased sperm production as a result of this exposure. Consult your physician who may perform a semen analysis and sperm count.

Question:
Have you ever had an operation on your testicles or hernia repairs in the lower abdominal region?
Behavior:
You may have reduced fertility. Consult your physician.

Question:
Do you drink more than 10 alcoholic beverages per week?
Behavior:
Consult your physician, you may have semen abnormalites.

Question:
Have you ever considered having a vasectomy as a method of birth control?
Behavior:
Vasectomy should be considered seriously. Consider that there may be some side effects that could lessen your fertility even if you had a reversal. Consult your physician.

Question:
Do you frequently take hot tubs, saunas or other chronic heat exposure.
Behavior:
You may have reduced fertility.

Question:
Can you name all of your sexual partners?
Behavior:
Multiple sexual partners exposure you to increased risk of AIDS, gonorrhea, herpes, pelvic inflammatory disease and other conditions which can lead to infertility, significant illness or even death. It is important to consider the consequences of your sexual activity.

Question:
Have you had difficulty in achieving and/or sustaining penile erections (potency) or sexual arousal (libido) sufficient to successfully initiate or complete sexual intercourse?
Behavior:
You could have a problem with the functioning of your testes.

Question:
Have you ever been treated for cancer or lymphoma?
Behavior:
You could have a low sperm count. Consult your physician.

Question:
Do you, following urination, continue to dribble a few drops of urine or stain your underwear with urine?
Behavior:
This might effect your general health and/or your potential fertility. You probably have an infection of the prostate gland. Consult with your physician, who will need to examine you and possibly prescribe antibiotics.

APPENDIX III

Questions - Recommended Behavior
Selected from questions submitted at Prevention of Infertility Workshop, June 19, 1987

Female

Question:
Do you feel that having children is very important to your goals in life?
Behavior:
You should develop five and ten year life plans that will include the opportunity to conceive and have children.

Question:
Have you considered the role of children in your marriage and come to an understanding regarding number of children and when you will have children?
Behavior:
If you are involved in a significant relationship, you should initiate discussion on these issues.

Question:
Have you had unprotected intercourse for over one year without becoming pregnant?
Behavior:
You may be infertile.

Question:
True (yes) or false (no), a woman is only fertile one day a month?
Behavior:
If you answered no, you may have a misunderstanding about the relationship between the timing of sex and pregnancy. Consult your physician, who will clarify this relationship.

Question:
Have you had a ruptured appendix and an appendectomy?
Behavior:
You may have pelvic adhesions reducing your fertility. Consult your physician.

Question:
Have you ever had profuse vaginal discharge associated with pelvic pain?
Behavior:
You may have had a pelvic infection. Consult your physician to evaluate this history of infection.

Question:
Did your mother take diethylstilbesterol (DES) while she was pregnant with you?
Behavior:
You may have an increased risk of pregnancy complications. Consult your physician for evaluation of DES exposure.

Question:
Is your weight significantly above or below what it should be?
Behavior:
Your fertility may be compromised. Consult your physician regarding a program for weight management.

Question:
Do you have a significant amount of pain with your periods or at the time of intercourse?
Behavior:
You may have endometriosis, a condition associated with infertility. Consult your physician.

Question:
Have you ever been treated for fallopian tube infection, salpingitis (pus tubes), uterine infection, or pelvic inflammatory disease?
Behavior:
Fallopian tube infection can cause blocked or damaged fallopian tubes that prevent pregnancy.

Question:
Are you currently using an IUD for contraception?
Behavior:
You are at increased risk of tubal infection which can cause infertility. Consult your physician regarding the advisability of removal and use of an alternative form of birth control.

Question:
Have you noticed any increase in the amount or thickness of hair on your face, chest or abdomen?
Behavior:
This might effect your general health and/or your potential fertility. You could have a hormone imbalance. Consult your physician who might perform laboratory testing to identify a particular abnormality.

Question:
Have you ever had an episode of abdominal pain, abnormal vaginal discharge, fever or bleeding within a few weeks of an abortion or delivery?
Behavior:
You may have had a fallopian tube infection.

Question:
Do you have a white or milky discharge from your nipples which can be increased with gentle pressure?
Behavior:
You may have an elevated prolactin level. Consult your physician for a simple blood test.

Question:
Can you name all of your sexual partners?
Behavior:
Multiple sexual partners exposure you to increased risk of AIDS, gonorrhea, herpes, pelvic inflammatory disease and other conditions which can lead to infertility, significant illness or even death. It is important to consider the consequences of your sexual activity.

Question:
Do you exercise vigorously (running, bicycling, etc) for more than 60 minutes daily?
Behavior:
You may be at risk for an ovulatory problem. If you menstruate less frequently than once very 40 days, consult your physician.

Question:
Has a sexual partner ever complained of burning on urination or pain at the time of ejaculation?
Behavior:
Your partner may have had a sexually transmitted disease he could pass to you. Consult your physician regarding evaluation for history of infection.

Question:
Do you smoke more than one pack of cigarettes per day?
Behavior:
Smoking may be associated with difficulty conceiving. Stop smoking!

Question:
Have you ever had a pregnancy in the fallopian tube (ectopic pregnancy)?
Behavior:
You may have fallopian tube damage.

Question:
Are you considering postponing childbearing beyond age 30 for work/school or other personal reasons?
Behavior:
Fertility decreases with age. You might wish to have children sooner.

Question:
Did you have your first menstrual period at the same time as your classmates?
Behavior:
If you had a delay of several years in the time of your first menstrual period, you are at risk to have problems with ovulation.

Question:
Do your mother and/or sisters have endometriosis?
Behavior:
You may have endometriosis, a condition associated with infertility. Consult your physician regarding evaluation for endometriosis and a discussion of future plans for pregnancy.

Question:
Did you begin intercourse before the age of 20, have greater than five previous sexual partners, or a sexual partner with a genital infection or discharge?
Behavior:
Some sexually transmitted infections can produce fallopian tube damage.

Question:
Have you had any operations on your cervix such as cone biopsy, cervical freezing or electrocautery?
Behavior:
Your cervical mucus quality may be poor, which may compromise your ability to get pregnant. Consult your physician for evaluation of your cervical mucus.

Question:
Have you ever had sexual relations with a man who you think might have been homosexual, bisexual or a drug user?
Behavior:
You are at increased risk for AIDS. Consult your doctor to decide whether you should have a test for AIDS.

Question:
Did your mother experience menopause before the age of 40 years?
Behavior:
You could also experience early menopause. Consult your physician.

Question:
Have you had two or more voluntary abortions?
Behavior:
Utilize effective birth control to prevent cervical injury, uterine scarring or pelvic infection from repeated abortions.

Question:
Do your menstrual periods last greater than 6 days, come more frequently than every 24 days, and/or require the use of both a tampon and pad togeter to maintain cleanliness during your period?
Behavior:
These factors are associated with a lack of regular ovulation.

Question:
How could one prevent getting venereal disease?
Behavior:
Limiting number of sexual partners. Douching. Using vaginal contraception (condom, diaphragm, foams/jellies), birth control pills, IUD, smoking, drugs.

Question:
Of the following, which do you think may effect your fertility: weight loss/gain, dieting, exercise, hormone pills, or stress.
Behavior:
All of these factors are capable of preventing regular ovulation.

PRECONCEPTIONAL HEALTH APPRAISAL

DATE _____

Place an "X" mark next to any item that is true for you.

I. NUTRITION: Do you:

____ Eat less than three meals some days
____ Practice vegetarianism (eat few or no meats)
____ Practice fasting (avoid eating for 24 hours or longer)
____ Eat laundry starch, clay or dirt on occasion
____ Vomit more than once a month
____ Take or plan to take birth control pills
____ Eat a special diet

II. SOCIAL HISTORY: Do you:

____ Have questions about children whose mother and father are blood relatives
____ Smoke cigarettes
____ Drink beer, wine or hard liquor
____ Work with lead or chemicals
____ Use lead or chemicals in hobbies or at home (such as oven cleaners, paint strippers, pesticides, ceramics)
____ Work with radiation or ever have X rays
____ Own a cat

Are You:

____ Age 16 or less
____ Age 34 or greater

III. FAMILY HISTORY: Does anyone in your family have:

____ High Blood Pressure
____ Diabetes ("Sugar" Diabetes)
____ Hemophilia ("Free Bleeders")
____ Jewish Background (Tay Sachs Disease)
____ Sickle Cell Disease or Trait
____ Birth Defects (such as heart, spine or other problems)
____ Mental Retardation
____ Cystic Fibrosis

Appraisal development supported by a grant from the Public Health Service, Office of Family Planning.
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NAME

Preconceptional Health Appraisal

IV. MEDICAL HISTORY: Do you now or have you ever had:

Genital Herpes
Gonorrhea
Syphilis
Epilepsy (seizures or spells)

____ Diabetes ("Sugar" Diabetes)

____ High Blood Pressure

____ Heart Disease

____ Other (such as PKU, Kidney Disease, Venereal Warts)

V. REPRODUCTIVE HISTORY: Have you had any of the following:

____ History of "female" surgery (ovaries, tubes, uterus, cervix)

____ History of an abnormal uterus or cervix

____ History of your mother receiving DES (a drug to stop miscarriages) when she was pregnant with you

____ Two or more abortions after 14 weeks of pregnancy

____ Three or more miscarriages
____ Five or more pregnancies

____ Less than 12 months since last birth

____ One or more infants weighing more than 9 pounds at birth

____ One or more infants weighing 5½ pounds or less at birth

____ One or more fetal deaths (stillborn)
____ One or more neonatal deaths (baby died before one month old)
____ One or more infants with a birth defect
____ One or more infants requiring a stay in an intensive care nursery
____ History of vaginal bleeding late in pregnancy

VI. DRUG HISTORY: Do you ever use:

____ Prescription Drugs

____ Drugs that do not need a prescription

____ Street Drugs
____ Vitamins
____ Birth Control Pills

VII. FOR YOUR DOCTOR OR NURSE

____ No history of rubella or immunization
____ Weight greater than 120% of ideal for height

____ Weight less than 85% of ideal for height

____ Hct less than 36% or hgb less than 12 gms

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APPENDIX V

Estimated Time-Line for Prevention of Infertility Program

FIRST YEAR:

- Development of questionnaire
- Development of related educational materials
- Select target populations and geographic sites
- Design system to implement program at the selected sites
- Design methodology to objectively study effectiveness
- Hire personnel

SECOND AND THIRD YEARS:

- Promotion of the program
- Apply questionnaire; counsel presons with risk factors; encourage appropriate behaviors
- Collect data
- Follow-up (acceptance; changes in behavior; acquirement of new knowledge)

FOURTH YEAR:

- Analyze follow-up data
- Determine future of program
- Make appropriate modifications in program
- Plan implementation on a wider scale if program is to be continued

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PREVENTION OF INFERTILITY

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"Although these are my enemies, whose wits are overthrown by greed, see not the guilt of destroying a family, see not the treason to friends, yet how, O Troubler of the Folk, shall we with clear sight not see the sin of destroying a family?"

Arunja to Lord Krishna

"All these observations call attention to our lack of understanding of several of the most basic events of reproductive biology."

Crowley WF, N Engl J Med
315:1607-1608, 1986

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Introduction

Inability to reproduce is now a cause of increased concern to men and women who, just a few years ago, focused instead upon contraception and career development. Such a shift is predictable given the aging of the post-World War II "baby boom" generation and the urgency of this large group to begin or complete a family. Despite these generational concerns, the enduring facts are that human reproduction is a highly evolved process in which opportunities and outcomes have always been matters of highly personalized circumstance and not necessarily matters of choice. Successful reproduction generally subsumes cooperation in the intricacies of mating, gamete production, fertilization, and ability of the conceptus to implant and prosper within the mother. Obviously, the many factors which can interfere with such complex and interrelated behavioral and biologic processes are better prevented than treated. In the limited light of current knowledge, the means and methods presently available to prevent some of the processes which diminish human fertility, and thus a part of individual and human potential, will be examined.

Procreation remains an elemental and essential human activity. Thus, fertility and the means to preserve fertility, can be considered in a large number of contexts: biological, cultural, psychological, economic, religious, philosophical, and medical, among others. Deterministic views, as embodied by Freud's epithet "Anatomy is destiny", lead only to gender"dependent nihilism. In fact, much can and should be done by individuals, couples, and society to preserve fertility. Along these same lines, overeager consideration of sentiments such as those found in Edna St. Vincent Milay's couplet,

"Whether we find what we are seeking
is idle, biologically speaking.

would lead to a spare, long-term minimalistic biologic view which has little room for personal and family imperatives of childbearing. These are heard in Sylvia Plath's bitter monthly keening,

"Spiderlike, I spin mirrors,
Loyal to my own image,
Uttering nothing but blood."

"Childless Woman"

In this analysis, we focus on identified factors which can diminish human reproductive potential and for which positive, practicable steps can be taken. Given the limited knowledge of the workings of reproductive biology and factors which undermine these processes (1), we also emphasize the need for further study and understanding in areas where the gains are anticipated to be greatest. We hope that the information presented here will assist in the development of well reasoned and considered personal and public agendas for solving the calculus of desired fertility.

Definition: Semantic and Biological

While unsettled terminology is one mark of an emerging area of study (2), the semantic imprecision and countervailing use of the terms "fertility", "fecundity", "infertility", "impaired fecundity", and "sub-fecundity" impedes scientific understanding and communication. Importantly, the resulting confusion can lead to needless anxiety and medical care for many couples.

Dictionaries refer to fertility simply as the ability to reproduce and suggest that fecundity is fertility in abundance. (3) Demographers often refer to fertility as crude rates of birth (4, 5) whereas reproductive statisticians propose to characterize fertility by multiple variables. (6)

Mosher and colleagues use "fecund" as a category consisting of women (and hence men) not surgically sterile. (7) They use sub-fecund to mean that there is physical difficulty in becoming pregnant, or that a health care provider has advised against pregnancy, or both. Thus, Mosher and colleagues use "fecundity" to mean "physically able" to reproduce while using "impaired fecundity" to describe anything less than full fecundity (sub-fecund, infecund, non-surgically sterile, or having a "long interval" since last pregnancy but not surgically sterile) (7).

The clinical or medical meaning of fertility is best defined by its obverse: infertility. Clinical infertility is defined as the inability to conceive after a year of regular intercourse in the absence of contraceptive use (7, 8). Although neither specific nor a true test of fertility, this definition is useful to facilitate evaluation, diagnosis, and possible treatment of either or both members of an infertile couple. Because, however, the inability to conceive is rarely absolute, the term "sub-fertility" is used by many clinical specialists. Such medical specialists have also taken the concept of fecundity to mean the "probability of conception in any given month for an individual couple" (8). Used this way, fecundity, or "average monthly fecundibility", connotes a measure of quantity derived from the number of conceptions divided by the total person months of exposure. (9) "Fecundibility" is a valuable concept which refers to measurement of fertility in relation to time, such as advancing age, or disease, such as after salpingitis. Conception delay is an adjunctive measure of "sub-fecundibility".

Corroboration of the non-specificity of the medical meaning of infertility comes from a recent study of couples unable to conceive after at

least one year of regular intercourse without contraception. (10) This study also suggests that the diagnosis of infertility has a low negative predictive value. A high proportion, 41%, of couples whose infertility was treated subsequently conceived, but so did 35% of untreated women. (10, 11) In this study, couples who became pregnant of various evaluations, such as hysterosalpingogram, were arguably assigned to the "untreated" group. (12)

Trussell and Wilson found that fully 23% of women in rural English parishes who married between the ages of 20 and 24 failed to give birth within the first two years of marriage, however, only 4.6% never had a child (13). Bongaarts estimated the monthly probability of conception in several populations of newlyweds who were mostly young and presumably close to the peak of their reproductive capacity (14): it takes a mean of 8-months for conception to occur and 14% of couples take more than a year to conceive. Correspondingly, for women of older ages, it would take longer to conceive. (11).

In this paper, we are primarily interested in individuals or couples retaining, rather than demonstrating, their ability to reproduce. Fecundity appears to be the best technical term for this as reversible contraception many temporarily impair fertility, but not fecundity. Therefore, we rely upon the definitions and terms set forth by Mosher and colleagues because these are most inclusive and increasingly are found in general usage. (Table 1)(7)

Epidemiology and Etiology

The extent and causes of reduced fecundity in even small populations is difficult to measure. Sample sizes are limited and knowledge as to whether or

not a person is able or unable to reproduce is uncertain. (7) Without thorough evaluation, the causes of non-surgical sterilization or impaired fecundity are impossible to determine. Further, couples medically evaluated for infertility differ from the general population of infertile couples. (15, 16) Because women and couples seen by physicians in the United States tend to be more frequently white and relatively young (15), causes of infertility in other groups can be underestimated.

Given these caveats, trends in United States fecundity and infertility can be characterized up until 1982. (17) Mosher and Pratt's analysis of the National Surveys of Family Growth data from 1976 to 1982 shows: (1) 2% of women are non-surgically sterile; and, (2) 5% of women were subfecund and another 1% had a "long interval" (3 years) after their last pregnancy. The percent of women or couples with impaired fecundity ranged from 2% at age 15-19 to 13% at age 35'39. Up to one in eight couples who were not sterilized, have a difficult time conceiving. (17)

More thorough analysis of data from 1965 to 1976 determines more marked differences of infertility among racial groups. (17, 18) During these years, the overall rate of infertility remained unchanged, however, estimated infertility in black women increased sharply so that by 1976 18% of black women and 9% of white women of reproductive age were infertile. Available evidence shows a strong association between sexually transmitted diseases, pelvic inflammatory disease, and infertility trends, especially in black women. (167) In 1976, 5-8% of 20-29 year old black women were estimated to suffer infertility attributable to sexually transmitted diseases. Among white women of similar ages, only 0.7-1% of infertility was ascribed to sexually transmitted diseases. (17, 18). This same predominance of infection as a cause of decreased fecundity in blacks has been noted historically as well. (19)

Additional evidence that sexually transmitted diseases are a primary cause of infertility comes from a World Health Organization sponsored collaborative study. The results of this evaluation of infertile couples in developed African, Asian, Latin American, and Eastern Mediterranean countries are listed in Table 2. U.S. findings are similar to those of other developed countries. (18, 21) Tubal infertility with tubal obstruction and adhesions is the single most common cause of infertility in each region, followed by male factors, and various causes of anovulation and endometriosis. As in other studies, combined multifactorial male and female factors in infertility occur in approximately 30-40% of cases. (22, 23) The African experience was distinguishable as fully 85% of African women diagnosed as subfecund had suffered some form of pelvic infection whereas endometriosis was rare. (24) These findings support the causal connection between sexually transmitted disease, other causes of pelvic infection, and reduced fecundity. Whatever the primary cause of infertility and subfecundity in a population, initiatives for reducing these problems should be cause-specific.

Prevention

"But since, both in importance and in time, health precedes disease, so we ought to consider first how health may be preserved and then how one may best cure disease..." (25)

Intelligent prevention of impaired fecundity "requires anticipatory action based upon knowledge of the natural history to make the onset or further progress of disease unlikely..." (26) To be optimally effective, preventive strategies must be based on knowledge of pathogenesis.

Leavell and Clark describe primary prevention strategies as those aimed at preventing entirely the disease process. This can be accomplished by

health promotion activities, specific medical methods of protection, or diagnosis and treatment of infection or other ills among transmitters. (26, 27). Secondary prevention aims at reducing morbidity once an infection or a disease has already been acquired. (26, 27) Examples are prompt recognition of possible symptoms of vaginal infection and pelvic inflammatory disease or epididymitis/orchitis by women and men respectively, followed by prompt care-provider evaluation, diagnosis and effective treatment according to current guidelines. Tertiary prevention requires rehabilitation once disability is present; for example, surgical attempts at restoration of fallopian tube or vas deferens function after salpingitis or vasectomy. Leavell and Clark suggest that specific aspects of the host, disease causing agents, and environment be considered at each level of prevention. "Team work" in health promotion with cross-communications between care providers, members of the community, and public health officials is also stressed. (26)

Both general health information and audience-appropriate programmatic instruction should be foundations of primary prevention. Knowledge of the fundamental facts concerning each potentially damaging process - its cause, treatment, and prevention are individual and community assets. (26) Further, understanding and appreciation of our "healthy" abilities, such as the ability to reproduce and produce families, should be universal. Everyone should comprehend, as much as possible, what is at stake when health is jeopardized. One innovative technique in regards to preservation of fecundity and providing family planning amongst teenagers, is asking them to play at making "time movies" in which they envision their lives and what they would value ten years in the future. Responsibility for appropriately

promoting such knowledge must be actively shared by parents, health care providers, educators, and possibly church authorities, as well as the mass communication media.

More specific examples of primary prevention for personal preservatives of fecundity include: (1) reducing risks of exposure to sexually transmitted diseases such as chlamydia and gonorrhea infections; (2) use of contraceptive methods which reduce risks of STD spread or damage; and (3) future development of vaccines and chemoprophylaxis protocols effective against common STDs. Immunization against infection is a widely recognized example of primary prevention. Case finding of community members exposed to STDs is another technique, which if rigorously carried out in appropriate circumstances, can primarily prevent STD mediated reproductive damage in as yet unexposed individuals.

Effectively done case finding is also an example of secondary prevention since it allows for early diagnosis and treatment of individuals infected but not yet damaged by chlamydia infection or gonorrhea. Community dissemination of knowledge regarding early recognition of diseases such as pelvic inflammatory disease, endometriosis or genital tract neoplasia in men and women can hasten possibly fertility preserving treatments.

Medical care providers require specific undergraduate and postgraduate training to improve recognition and therapy of diseases which threaten fertility. The Center for Disease Control's initiation and support of regional training programs offers many care providers the knowledge to recognize and treat fertility threatening STD syndrome; information which is not otherwise systematically provided to U.S. health professionals. Greater

general recognition that C. trachomatis causes severe reproductive tract damage is an immediate goal, which if accomplished would ensure earlier detection and treatment of these infections in men and women.

As noted, tertiary prevention is based on repair and rehabilitation. This is the least desirable means to "prevent" lost reproductive potential. Fertility enhancing treatment is always expensive and not necessarily effective. Estimates for monetary costs range up to $30,000 for each successful term pregnancy made possible by surgical fallopian tube repair. (28) Widely publicized in vitro fertilization procedures cost between $4,000 and $6,000 for each treatment cycle, with successful pregnancy occurring only in a portion of treated couples. Treatments to improve sperm "quality" are frequently unsuccessful and difficult to evaluate. Further, successful fertility therapies require great expenditures of medical resources with application of many skills, including nursing and psychotherapy if all the discomforts of infertile couples are addressed. The nonmonetary personal, familial, and societal losses caused by lost fertility are incalcuable. Clearly infertility is better prevented than treated.

Once fecundity is impaired, there is great impact upon emotional well-being and perceived quality of life. (27) Curran's ingenious example of aspects of prevention for impaired fecundity due to sexually transmitted promoting such knowledge must be actively shared by parents, health care providers, educators, and possibly church authorities, as well as, the mass communication media. diseases (STDs) is presented in Figure 1 and Table 3. (27). The relative success of various strategies for primary preservation of fertility is likely to depend upon individual approaches based on specific

processes which can impair fecundity. Successful strategies will likely differ across populations and among individuals. Even though primary preventive stratagems are not likely to be absolutely "most cost-effective" in the public health setting, they are clearly the most desirable for each individual and society in the long run. (27)

Age and Fecundity

"You will observe that when a woman begins to (bear children) at an early period, as at fifteen, and has her children fast, that she seldom (bears children) longer than the age of 30 to 35. Therefore, we may suppose either that reproductive tract organs are then worn out, or reproduction is over. If a woman begins later, as at 20 or 25, she may continue to (bear children) to the age of 40 or more. And there are now and then instances of women who not having conceived before, have had children as late in life as 50 years and upwards. After that, few women (bear children), even if they should not have become pregnant before. Therefore, there must be a natural period to the power of conception..."

John Hunter, 1787 (29)

Fecundity of couples is determined primarily by the age of the woman and the duration of the marriage. (11, 30) That fecundity decreases as maternal age increases is well established (11, 30-33), although such study results have elicited controversy (34). Analysis of historical records from a variety of "natural" populations in which reproduction was considered unfettered by "family limitations", as well as recent experiences of women receiving

artificial insemination for treatment of infertility, demonstrate strikingly similar patterns of fecundity. (11) Although fertility varies greatly among different populations, the age-related patterns of decline are nearly uniform. (35) Compared to that of women age 20 to 24, fertility is reduced by an average of 6% for women 25 to 29, 14% for those 30 to 34, and 31% for women 35 to 39, with much greater decline thereafter. (11) Such statistics are not nearly as discouraging, or frightening, as has been thought in the recent past: many couples simply take longer to conceive in later life than they would have at a younger age. Indeed, in the absence of disease processes causing impaired fecundity, most women in their mid-thirties are still quite able to ultimately conceive. Estimates from a Mormon group show that even women in their late thirties bear children at 90% of their base rate. (11) In most populations, childbearing becomes much less likely after the prospective mother enters the fifth decade of life. (11, 30) Hutterite women more frequently continue reproduction into the fifth decade of maternal life, but their fertility rate is 10-fold less than the peak at 20-24 years. (30)

Male fertility declines very slowly until the sixth decade of life; among a Mormon population at age 50 to 54 years, fertility was 73% that of the early 20's. (11) Male fertility falls to less than half the basal rate only after age 55, and male postpubertal peripheral testosterone levels remain relatively constant until approximately age 70. (36) (37) With increasing age there is wider andgrogen level variation among individuals. Some evidence suggests that sexual activity contributes to the maintenance of plasma testosterone levels in elderly males. (36) Even if plasma testosterone levels are maintained, spermiogenesis and parameters of semen evaluation may decline with advancing age. Testicular steroid secretion does not appear directly linked with the so-called male climacteric. (36)

Age-related impaired fecundity suggests that a biological basis underlies the limits of human procreation. The basis for these limits, however, remains poorly understood. Its exploration will lead to further physiologic understanding of these complex, highly evolved, reproductive processes. (38) Teleologic speculation suggests that differential decline of female and male fertility optimizes chances for conception while reducing the overall risk of birth of children with chromosomal abnormalities (prominently trisomies after age 35) and severe congenital abnormalities (after age 42-45). (30) Other reproductive, medical, behavioral, and sociological factors also influence chances for childbearing.

Interestingly, fecundity rates decline not only with the ages of the spouses but also with marriage duration in both historical and contemporary data. (11, 30) Menken, Trussell and Larsen consider this to be caused by a combination of decreased sexual activity and cumulative reproductive impairment associated with successive pregnancies. (11) Other factors reflect contemporary trends more strongly. High childlessness and low fertility in U.S. caucasian women 45 years ago was attributed to delayed marriage and sexual relations. (11) Today, sexual activity precedes marriage for much of the population, and the timing of parenthood within and without marriage has also become more varied. Among other factors, the perceived availability of effective contraception and abortion have made delay of childbearing without abstinence or delayed marriage relatively easy. These changes appear linked to changes in sexual behavior, including earlier onset of sexual activity (coitarche), and increased total number of sexual partners and exposure to sexually transmitted diseases. Such increased sexual exposure, in turn, increases risks of impaired fecundity from pelvic inflammatory disease, ectopic pregnancy, and the risks of birth control techniques. The importance

of these intercourse-related influences on fecundity has been increasingly acknowledged even as new determinants are added which further affect the calculus of fecundity for modern couples. (39)

That the current increased use of infertility services was predictable as the post-World War II "baby boom" generation aged and postponed childbearing to allow pursuit of career goals, and suffered complications of STDs as well, does not diminish the discomforts or poignancy of those men and women effected. (11, 39) These presently felt concerns have prompted reexamination of planning trends for career and family. DeCherney and Berkowitz suggest that contemporary U.S. women should "devote" the third decade of life to childbearing and the fourth to career development rather than the converse. (38) Resolution of the predicament of declining fecundity with increasing age, primarily in women, and contemporary out of home employment practices requires both public and personal knowledge and discussion and adaptation.

Infection and Ectopic Pregnancy

Among sexually active women, the greatest single cause of impaired fecundity is damage to the fallopian tubes, and possibly ovaries and endometrium, caused by pelvic inflammatory disease (PID). (11) PID is an incompletely understood disease involving bacterial infection ascending from the lower genital tract through the endometrium (endometritis) to the fallopian tubes (salpingitis), and possibly to the ovaries (oophoritis) and pelvic peritoneum (peritonitis). Current knowledge suggests that reduced fecundity due to PID stems primarily from physical damage to the fallopian tubes (40, 41, 42): peritubal adhesions impair tubal mobility which is essential for fallopian tube recovery of the ovulated ovum. Intratubal obstruction or deformation blocks or impairs gamete transportation and

fertilization. Bacterial products or by-products of inflammation may also cause transient impairment of oviduct and endometrial function. Of increasing interest are the possibilities that subclinical cervical, endometrial, tubal, and possibly ovarian infections with various Mycoplasmas and other microorganisms may also play roles in reducing fertility or fecundity. (43) Recurrent infection is of great significance: approximately 13% of women with laparoscopically diagnosed salpingitis develop bilateral tubal obstruction subsequent to an initial episode; figures for repeated episodes are 22% after two episodes and 75% after three or more. (42)

Although more important in developing countries, other genital tract infections can greatly reduce fecundity. Postpartum infection (puerperal sepsis), post-cesarean section infection, post-abortal infection, and infections after many other obstetrical or gynecologic procedures may also cause tubal damage. African women, in particular, suffer from postpartum and post-abortal infection. (24) In the U.S., a large review of women who suffered febrile morbidity after cesarean section did not demonstrate subfecundity unless there was a tuboovarian abscess. (44) On the other hand, Trimbos-Kemper's review implicated postpartum and postoperative pelvic infection in the pathogenesis of tubal infertility. (45) Safe birth practices, surgical technique, asepsis and antisepsis along with appropriate use of prophylactic antibiotics in selected patients is crucial to prevention of pelvic infection and subsequent decreased fecundity worldwide. (46, 47).

Microbiologic causation of PID is complex and varies with geography and groups of women studied. However, most non-puerperal and non-post-surgical cases are brought about by one or more sexually transmitted diseases (STDs). These principally include Neisseria gonorrhoeae and Chlamydia trachomatis. (41, 48, 49) Other microorganisms, including bacteria commonly found in the

cervix or vagina, can be involved. PID occurring in the absence of detectable sexually transmitted disease is more common after instrumentation (biopsy, curettage, IUD placement, etc.) or after birth (puerperal sepsis). Nevertheless, the preponderance of microbiologically evaluated, community-acquired PID is mediated by one or more sexually transmitted diseases. Between 1965 and 1975, reported cases of gonorrhea tripled and then remained at a level of about 1 million reported cases per year for 5 years; these numbers have subsequently declined somewhat. (50, 51) Gonorrhea case reporting is obviously incomplete and chlamydia infection is not presently reportable, even though it is the most common single cause of PID in different locales. (41, 52)

Not all cases of gonorrhea or genital chlamydia infection lead to PID. Acquisition of gonorrhea and/or chlamydia genital tract infection is associated with at least a 10-20% risk of developing clinically recognized PID. (53) Given the frequency of STDs and a noted increased risk of PID in younger women, Bell and Holmes calculate that 3% of sexually active teenagers and somewhat less than 1% of women in their early to mid-twenties will suffer pelvic inflammatory disease each year. (54) This calculation fits the experience of young sexually active U.S. urban women. (54) Using age-adjusted risks from Swedish women, Westrom took these projections a step further and calculated cumulative rates of post-PID sterility (from salpingitis) in a hypothetical cohort of 100,000 women born in 1950. (Table 4) He estimates that about 2500 women (2.5%) will be unable to conceive on account of post-salpingitis tubal damage at their 30th birthday. (55) Although theoretical, this calculation approximates the prevalence of tubal infertility in various populations. (11)

United States figures on the frequency of pelvic inflammatory disease are also compelling. In the 1982 National Survey of Family Growth, women were asked whether they had ever had pelvic inflammatory disease. The proportions of women answering positively rose with age to a maximum of 20% for women in their early thirties and then declined. (56) In this study, pelvic inflammatory disease was twice as common among non-whites as in whites, confirming the 2.5-fold racial difference noted by Washington. (57)

Women with salpingitis also suffer impaired fecundity because of ectopic pregnancy. Approximately one-half (30-60%) of cases are associated with evidence of salpingitis. (58, 59) The frequency of tubal pregnancy increases 6-10 fold subsequent to an episode of documented salpingitis. (42, 58) In the last 15 years, rates of ectopic pregnancy have increased 2- to 3 fold, likely as a direct consequence of increased occurrence of salpingitis. (59, 60)

A single cohort study of women with ectopic pregnancy suggests that women who douche weekly are at significantly increased risk for ectopic pregnancy than are women who never douche. (61) It has also been proposed that douching may be a risk factor for pelvic inflammatory disease. (62) If frequent douching is confirmed as predisposing to ectopic pregnancy and/or PID, then eliminating or reducing this practice could be a relatively easily accomplished means to reduce risks of impaired fecundity due to these disorders.

It is likely that some of the increased occurrence of ectopic pregnancy is due to improved means of diagnosis using improved biochemical tests to do test pregnancy. Reviews of large recent series now show that in women who wish continued fecundity, careful salpingostomy without removal of the fallopian tube is associated with outcomes better, or no worse, than if the

affected tube was removed. (59) Similarly, new information suggests that some tuboovarian abscesses may be safely drained rather than excised in combination with intensive antibiotic therapy. These approaches are justified only where medical and surgical care is readily available.

Current knowledge of infectious causes of male impaired fertility is scant. The majority of recent reviews of male infertility do not even mention sequelae of STDs. Recently, the possibility that asymptomatic male accessory genital gland infection or colonization with a variety of organisms, including Mycoplasma and Ureaplasma species, has captured much interest. No clear relationships between reproduction and seminal fluid, and/or microbiologic findings have been presented. (63) Despite this, many infertile couples are treated unnecessarily with antibiotics. (64)

On the other hand, observations from the preantibiotic era make it clear that various genital tract infection syndromes are associated with male infertility. Pelouze noted that 10.5% of men with a history of gonoccal urethritis and that 40% of men who have bilateral epididymitis demonstrated infertility (65). Recent studies examining the possibility of increased occurrence of male serum anti-sperm antibodies are poorly controlled and conflicting. (66, 67, 68) Past studies also suggest that 30% of males with bilateral mumps orchitis develop azoospermia (69).

Interestingly, two reports from Nigeria describe substantial male infertility ascribed to poorly or untreated sexually transmitted disease. (70, 71) Awojobi describes 164 out of 510 men evaluated for infertility with chronic epididymitis (32%) (70) Eight-five percent of these men had a definite history of sexually transmitted urethritis. Either azoospermia or oligospermia was present in all of these patients. Other sequelae of

undefined urethritis which could interfere with fertility include urethra stricture and perineal fistula. (71) Modern prospective studies of reproductive tract functions and fertility subsequent to genital tract infection in male are notably lacking; such studies should be expedited. Both symptomatic and asymptomatic genital tract infections in men must be identified and treated so as to prevent infection with sexual partners.

Obviously, prevention of sexually transmitted diseases in men and women is of primary importance in preventing loss of fecundity. Prevention of STDs is a large and diverse subject which goes beyond the scope of this paper; useful reviews are referenced (72, 73). A separate manuscript "Prevention of Sexually Transmitted Diseases in Women" is appended. In summary, effective public health initiatives aimed at STD and fecundity loss prevention in men and women include efforts in seven main areas (72):

1. Health education
2. Disease definition
3. Optimal treatment
4. Partner tracing and patient counselling
5. Clinical service
6. Training
7. Research, including social, psychologic, and biologic aspects of STDs

In addition, studies increasingly focus on behavioral aspects of STD acquisition and prevention. Aspects of individually enacted "personal prophylaxis" against STDs and possible fecundity loss have recently been analyzed. (74, 75) Primary principles for sexually active individuals include: (1) developing a discipline of self care; (2) restricting choices of sexual partners; (3) use of oral contraception with routine use of condoms as

adjunctive protection; (4) periodic STD screening; and (5) prompt medical care if symptoms develop. (64-66). Clearly, there is need for increased rigor and efficacy in carrying out and promulgating proven concepts, as well as development of new workable approaches. (75) These will likely include consumer oriented "home" tests for STDs, increasingly explicit public education efforts by public and private issue-oriented groups, patient derived demands for optimal care, and improved contact tracing and expanded multi-targeted research. It is crucial that these multifaceted efforts be focused on STD prevention in sexually active teenagers and young adults. Younger individuals have the highest rates of STDs and PID, and the most to lose from disease-induced impaired fecundity. (54, 77)

Tuberculosis

Although relatively rare in North America, in developing countries genitourinary tuberculosis involving female or male genital structures is a common cause of infertility and sterility. In the male, epididymal, vasal, and/or prostatic involvement may lead to fibrotic stricture with azoospermia or complete loss of function. Tuberculosis causes up to 14% of male infertility. (78)

Fallopian tube involvement is nearly universal in female genital tract tuberculosis and causes generally irreversible destruction and loss of tubal function. Endometrial infection occurs in about one-half of cases and cases involving intrauterine scarring and synechia (Asherman's syndrome) with subsequent infertility.

Because restoration of fertility is very difficult after most cases of genital tract tuberculosis, primary prevention requires that up to date prevention, control, and treatment measures be available and enforced as

recommended by public health authorities. (78) Leavell and Clark give a classic description of how primary, secondary and tertiary preventive techniques, as well as socioeconomic improvement, aid in the control of tuberculosis. (27)

Endometriosis

Although common, the pathogenesis of endometriosis and mechanism(s) of decreased infertility associated with this disease remain poorly understood. Endometriosis remains a disease of hypothesis (79). It is possible that there may be several processes which account for the development and morbidity of endometriosis. Endometriosis is characterized by the presence of endometrial tissue outside of the uterus. The ovaries, fallopian tubes, pelvic peritoneum, and visceral peritoneum are the most common locations of heterotrophic endometrium but other sites, such as pleura, lung, and lymph nodes, have been reported. (79) Endometriosis afflicts approximately 7-17% (range 4-50%) of menstruating women. (80) When symptomatic, the process is classically characterized by the triad of dysmenorrhea, dyspareunia, and infertility. Expression of each varies and correlates poorly with the physical extent of endometriosis. Kistner considered that fully 30-40% of women with endometriosis are subfecund. (81) Evidence of endometriosis is frequently found in women with otherwise unexplained impaired fecundity.

Suggestions as to how endometriosis impairs fecundity are multiple and not mutually exclusive. They include: interference with ovulation, ovum transport, or implantation or induction of early spontaneous abortion. (82, 83) There is clinical and laboratory animal evidence supporting each of these mechanisms. These processes may be mediated in turn by physical scarring, augmented phagocytosis of male or female gametes by increased

numbers of activated peritoneal and/or tubal macrophages, altered tubal or ovulatory or corpus luteum function because of altered prostaglandin homeostasis or by autoimmune phenomena. (82, 84) Certainly, other mechanisms could be considered. Because the precise mechanisms causing infertility in conjunction with endometriosis remain ill-understood, prevention is difficult.

The histogenesis of the disease process itself is also not completely understood. With rare exception, it is only ovulating and menstruating women who develop endometriosis. Cyclic, usually prolonged, estrogen-progesterone stimulation with ensuing menstruation is usually essential for endometriosis to occur. Remarkably, endometriosis is, in rare instances, reported in post-climacteric women with no evidence of estrogen activity, and even in chromosomally normal males.

Some women may be at increased risk. Genetic predisposition for initiation and propagation of endometriosis has been well documented. (85) Peritoneal remnants of embryonic reproductive tract (paramesonephric duct) structures are highly variable in extent and retain a multipotential ability to differentiate into endometrial, cervical, or tubal epithelium-like structures. (85)

In general, proposed theories explaining the histogenesis of endometriosis suggest: (1) that viable endometrial cells or tissue are transported directly and "explanted" in their pathologic location; (2) that endometrial tissue arises in situ from local tissues, or (3) that a combination of these processes occurs. Of these possibilities, the first has the most support and offers the most powerful means of prevention. Many observers have noted bits of endometriosis within pelvic or other lymphatics "downstream" from the uterus. Vascular spread, primarily to the lung, is also possible and could account for rare cases where endometriosis is noted in

diverse bodily locations. Pelvic endometriosis is much more common and has been linked to retrograde menstruation. (86) Past or anecdotal evidence has suggested that intraabdominal spillage of menstrual fluid during menses occurs in roughly one-third of ovulating women. Blood has been detected in peritoneal fluid of 90% of 52 women with patent fallopian tubes undergoing laparoscopy in the peri-menstrual period. (84) A larger study in which elective laparoscopic sterilization was performed during menstruation showed that retrograde menstruation occurs in up to 78% of ovulating women (57 of 75 women, ages 26-48). (87)

It is well established that endometrial tissue can be transplanted to other areas of the body in experimental animals. (85) In addition, endometrium may be inadvertently transported and implanted during surgical procedures involving the uterine lining or uterotubal junction. Multiple experiments establish that cast off endometrial particles are viable, and can implant intraperitoneally or within abdominal wounds. (79, 85)

While Sampson's theory of retrograde menstruation seems both intuitive and obvious, matters are likely more complex. Although endometriosis can cycle histologically under the influence of ovarian steroids, much evidence now suggests that endometriosis is different from uterine endometrium in a number of ways, including: (1) electron microscopic appearance, (2) nuclear and cytosolic steroid binding and failure of estrogen and/or progesterone to modulate steroid receptors, (3) prolactin secretion, and (4) 17 B-hydroxysteroid dehydrogenase activity in vitro. (88)

Other theories certainly deserve further exploration. Since Gruenwald's embryologic experiments of pathogenesis, there has been scant elaboration of the celomic metaplasia hypothesis of endometriosis. More importantly, evidence now shows that non-cellular constituents of menstrual fluid are also

capable of inducing endometriosis-like changes in perineal tissue. (89) Further, pelvic infection appears linked with endometriosis. Whether this is a casual or epiphenomenal relationship is yet to be determined. Fully 29 of 32 women with mild endometriosis had peritubular adhesions suggestive of past salpingitis. (87) Schmidt suggests that endosalpingosis (endometrial tissue in the fallopian tube) may facilitate ascending genital tract infection and that implants of endometriosis may become the seat of abscess formation. (88) Fully blocked tubes, from any cause, are experimentally associated with decreased endometriosis. (85)

Schemes for prevention of endometriosis are based upon understanding the etiological mechanisms of the disease process. We have seen these to be incompletely understood and not all-inclusive as endometriosis appears multifactorial. Thus, the suggestions for prevention are primarily theoretical.

"Low-dose" oral contraceptive agents suppress ovulation and produce an "atrophic" endometrium demonstrative of a progestin effect which bleeds little with monthly pill withdrawal. Thus, low-dose oral contraceptive tablets may be reasonably offered in the absence of contraindications to individuals at high familial risk for endometriosis. Certainly, the choice of oral agents for contraception is theoretically strengthened if the individual woman is considering delaying further pregnancies for several years. Possible prevention or amelioration of endometriosis by prolonged or periodic use of oral contraceptives demands specific study.

Along these same lines, many care providers suggest that early and repeated pregnancies will prevent or delay the onset of endometriosis. These recommendations are based on anecdotal claims suggesting uniform improvement of endometriosis during pregnancy. These claims have been repudiated. (85)

Care should be taken to avoid "spilling" menstrual fluid onto peritoneal structures or open wounds such as episiotomy or laparotomy wounds. Endometriosis at both abdominal and episiotomy wound sites has been reported. Similarly, hysterosalpingograms should not be performed during menstruation even though it is known that many women pass menstrual fluid through the fallopian tubes, in any case. Importantly, young women with congenital abnormalities which could impair menstrual afflux, such as imperforate hymen, complete vaginal bonds, or uterine abnormalities with occluded cervices should receive reparative surgery before development of hematocolpos, hematometra, hematosalpinx, and possible endometriosis. Care should be taken during surgery, cautery, or cryosurgery on the cervix to prevent stenosis with subsequent obstruction of menstrual drainage and potentially increased retrograde menstruation. Much less certain is the widely given advice not to "stopper" the vagina with menstrual tampons when flow is heavy. Perineal pads are a practical alternative.

Sampson and Ranney both recommend performance of fallopian tube ligation well away from the uterotubal junction so as to avoid endosalpingosis on the basis of anecdotal information. (85, 86) Overall, use of low-dose oral contraceptives and expeditious reconstructive surgery in females with obstructive genital tract anomalies appear most important in prevention of endometriosis. Further recommendations have been made. (85) Agents such as Danazol and LRF analogues appear effective as treatment for endometriosis but, due to toxicity, have no role in prevention.

Cervical Factors

Cervical mucous is a complex hydrogel which is produced by cells located in folds of the endocervical canal. Except at midcycle, the macrumoleus of

cervical mucous are densely cross-linked and act as a barrier or "plug" which excludes spermatozoa from entering the endometrial cavity. At midcycle (around the time of ovulation), the composition of cervical mucous changes so that sperm transport through the cervix into the endometrial cavity is facilitated. This complex change is under hormonal control involving both ovarian hormone production and endocervical cellular responses. If these events do not occur, fertilization and pregnancy become much less likely, especially in the presence of other causes of impaired infertility such as a low sperm count. (90) Less commonly, insufficient mucus production due to physical destruction of endocervical folds during operative procedures, such as extensive cervical core or excision biopsy, traumatic cervical dilitation or obstetrical laceration repair is also associated with evidence of decreased sperm transport.

Importantly, much introgenic endocervical damage can be prevented by avoidance of unnecessarily extensive core biopsy and by keeping in mind the possibility of endocervical damage whenever the cervix is surgically manipulated. Cervical surgery should be avoided entirely for "chronic cervicitis" since this condition is most likely caused by medically treatable infection. It is highly likely that infection and inflammation can also interfere with endocervical function. The influence of microbiologically defined endocervicitis or sperm transport and other cervical functions remains unstudied.

Macrophages

Intraperitoneal and intratubal macrophages may play physiologic roles in modulating granulosa-luteal cell progesterone production. (91) These macrophages occur in elevated numbers during menses in the presence of patient

fallopian tubes, possibly due to release of chemotactic or irritating substances from retrograde menstruation or infection. (92) Macrophages are thought to destroy male and female gametes and play roles in adhesion formation. Elucidation of quantitative and/or qualitative differences in these metabolically active cells in association with even mild endometriosis or pelvic inflammation could allow for prevention of tubal infertility on the basis of these factors.

Hyperprolactinemia: Physiologic and Pathogeneic

In all mammals, including humans, lactation is a key link in the reproductive cycle. (93) Ovulatory suppression prevails during nursing and serves as a primary means of birth spacing for humans. (94, 95) The degree and duration of postpartum lactational infertility are determined by many factors, including frequency of suckling and use of supplementary feeding. (95) Modern U.S. women who breastfeed exclusively may have prolonged lactational amenorrhea. (95) Prolactin is the key lactogen hormone and the duration of puerperal infecundity correlates with overall prolactin levels. Prolactin levels in turn correspond to the frequency and duration of suckling. (96) Elevated levels of prolactin suppress ovulation by effecting both hypothalamus-pituitary and intraovarian processes. (93) Puerperal lactational infertility continues for up to 3-4 years in !Kung women who suckle their children frequently and exercise strenuously gathering food. (97) Rapid weaning restores ovulatory function in the vast majority of postpartum women regardless of the duration or intensity of breastfeeding. Postpartum lactation is not associated with any long term fecundity impairment.

Hyperprolactinemia is an increasingly appreciated phenomenon which is identified as a cause of infertility in up to one-third of fully evaluated women. (98) Further, approximately one in five secondarily amenorrheic women have hyperprolactinemia and approximately one-third or more of these have pituitary adenomas. (99) Hyperprolactinemia is associated with impaired fecundity in the presence and absence of galactorrhea. Relative hyperprolactinemia is the biochemical common denominator of galactorrhea syndromes. (100) Consistently hyperprolactinemic women are almost always infertile. (98) Excess or disordered secretion of prolactin impairs the hypothalamic-pituitary-ovarian axis at each of its levels and can interfere with conception in complex ways.

Hyperprolactinemia was predicted as a cause of male hypothalamic hypogonadism and infertility several years before clinical cases were described. (101, 102, 103) Although rare in comparison with female cases, hyperprolactinemia in men is associated with decreased levels of testesterone, markedly decreased spermatogenesis, and even osteoporosis. As in women, male hyperprolactinemia can be ameliorated by removal of associated causes and/or bromocriptine administration. (104)

Causes of hyperprolactinemia are diverse and may not be easily prevented. The origins of primary causes such as prolactin-secretion pituitary adenoma, and "idiopathic" hyperprolactinemia remain poorly understood. At least 50% of patients evaluated are demonstrated to have evidence of pituitary tumor. Even though case-control epidemiologic studies in women suggest a relationship of past oral contraceptive use with galactorrhea, multiple other epidemiologic, clinical, and endocrinologic studies do not. (98, 99))

Numerous secondary causes of hyperprolactinemia also remain incompletely understood but are amenable to prevention. Various medications may cause hyperprolactinemia on the basis of relative dopamine antagonism. Phenothiazine-like drugs (chlorpromazine, etc.) butyrophenones (haloperidol), resperine derivatives, alpha-methyldopa, tricyclic antidepressants, and amphetamines are implicated in hyperprolactinemia and may be avoided or given in reduced amounts if fertility is an overriding concern. If continued drug use is indicated, then bromocriptine, a dopamine agonist, can be given to foster fecundity. Overzealous breast stimulation during lovemaking or other causes of chest wall stimulation in both men and women have been implicated in hyperprolactinemia in rare instances. Duration of hyperprolactinemia coincident with hypothyroidism, cirrhosis, renal failure, and hypothalamic disease is determined by the outcome of the primary process.

Exercise

There is considerable accumulated epidemiologic, endocrinologic, and clinical evidence that regular, strenuous exercise alters menstrual function, temporarily impairs fecundity and may predispose to osteopenia in women. (104-115) Gonad steroid and sperm production may also be altered by rigorous training in males. These changes have not, as yet, been associated with reduced fertility. The frequency of amenorrhea or oligomenorrhea among women participating in a variety of activities varies from 2-51% as opposed to 2-5% of more sedentary women. (109) In a prospective study of women with previously normal ovulation and luteal function, fully 87% developed abnormality of these reproductive functions when engaged in a strenuous exercise program. (108)

Menstrual irregularities are present in relatively high percentages of female runners (110), ballet dancers (106), and in women active in a variety of other physically demanding sports. (107) Hormonal abnormalities described in these women include disordered gonadotropin release and levels, decreased estrogen levels, corpus luteum inadequacies, and complete anovulation. (111-114, 116) Abnormalities appear greatest when exercise is most intense or when training is becoming more rigorous. (116, 117) Ellison and Lager suggest that even moderate exercise by recreational women runners (average 12.5 miles per week) reduces overall progesterone levels but does not delay luteal progesterone rises suggestive of ovulation. (111) Loucks has correctly emphasized the need for controlled studies in which nutrition, body fat composition, psychologic stress and "gynecologic age," age from menarche, are concurrently assessed. (117)

Mechanisms of altered reproductive physiology associated with strenuous exercise regimens are not completely understood. Some authorities hypothesize that these and other reversible endocrine effects are adaptations to "training" which are analogous to cardiorespiratory effects. (118) Specifically, it is proposed that lower levels of gonadotropins, hypoestrogenemia, luteal phase shortening, anovulation and infertility are responses to "hypothalamic conditioning" which serves a physiologic "purpose" for the individual. (118) Because it is known that prolactin levels rise immediately with exercise, it has been suggested that exercise induced disordered prolactin release is the primary agent for impaired fecundity. (117)

At this time, little information exists on the relationship between exercise-associated menstrual alterations on long term infertility or permanently impaired fecundity in men or women. Shangold and Levene reported that 10% of 394 marathon runners noted post or present impaired fecundity. (114)

Although this figure is not different from the normal populations (119), the majority of women in Shangold's study were using contraceptive and may not have tried to become pregnant. (114) Thus, this study may have underestimated infertility among these women. (115)

A recent retrospective study by Green and colleagues gives more relevant perspective. (115) Three hundred and forty-six women with evidence of ovulatory failure were interviewed regarding exercise patterns along with a cohort of fertile women. Vigorous exercise for an hour or more per day was reported more commonly in nulligravid cases (n=187) then by primiparous controls. The differences were not seen among infertile women who had previously been pregnant (secondary infertility). Importantly, vigorous exercise for an average of less than one hour per day was not associated with either primary or secondary infertility. (115) In this study, having a weight for height ratio of 85% or less than ideal was associated with infertility and with ovulation dysfunction. (115) Controlling for weight did not alter the association of extreme exercise and primary impaired fecundity, suggesting exercise exerts its putative effects independent of weight loss. (115)

Importantly, reversal of exercise-induced menstrual changes is well established. (108, 116) Given that menstrual abnormalities associated with subfertility are increased while training effects are being first achieved, normal menstrual function may return after conditioning is stabilized. (120) Barring that, Prior and colleagues empirically recommend training be reduced in 10% increments. (120) She further recommends body fat composition be "adjusted" or maintained at 18-20%. (120) This is likely too low a proportion since Frisch and others estimate that fat must comprise at least 22% of body compositions for maintenance of ovulation. (122)

Much remains to be understood about adaptations to increased or extraordinary fitness. The influence of body composition on puberty and reproductive function also remains to be elucidated. (123) In any case, reproductive hormonal changes associated with athletic training in females appear readily reversible and should not be construed as a reason to avoid or curtail athletic training. (121) Further study is required to define and perhaps modify risks of bone mass loss in females who exercise strenuously. (121)

Nutrition and Fecundity

"...and let your soul delight itself in fatness."

Isaiah 55:2

It is generally accepted that sexual maturation and continuation of cyclic ovulation depends upon achieving and maintaining an adequate amount of body fat as a proportion of total body mass. (122, 124, 125) Fatty tissue appears to directly influence reproductive maturation and function in both sexes by metabolizing both androgens and estrogens which, in turn, influence the central nervous system, hypothalamus, pituitary and reproductive tract organs in complex ways. (122, 125) Too little and (much less commonly) too much adipose tissue have each been associated with impaired fecundity.

The extensive and interwoven relationships between exercise, food, body mass and fat, fecundity, and reproduction were first described in a common sense way by Darwin who noted in domestic animals that (1) well fed animals were more fertile than poorly fed or wild animals; (2) "hard living" retards the period at which animals conceive"; (3) the amount of food modulates the fertility of the same individual; and (4) it is difficult to fatten a cow that is lactating. (126) Frisch supports much endocrinologic evidence with

teleologic and evolutionary arguments. She points out that completion of pregnancy and lactation requires approximately 50,000 calories and that this is roughly the amount of energy most normal women (26-28% body fat) possess in body fat. (122) Because fat is the most labile and sustainable source of body energy, possession of adequate fat stores serves as a physiologic "precondition" for conception and pregnancy. This would offer selective survival advantages. (122, 125) One conception of how multiple factors affect body mass and fat is depicted in Figure 2. Recognition of the biologic importance of body mass and fat, nevertheless, is somewhat at odds with current social trends which dictate the desirability of a svelte, yet muscular body often maintained by food restriction and considerable vigorous exercise. (127, 128)

Weight loss need not be dramatic to reduce fecundity. Loss of 10-15% of normal weight for height delays menarche, retards puberty and causes secondary amenorrhea and infertility in post-menarcheal women. (125) Bates and co-workers note that many women seeking infertility services practiced caloric restriction and still "appeared" normal. None demonstrated stigmata or history of a recognized eating disorder; all had merely "dieted." (127) Extreme weight loss results in the more complex and potentially lethal metabolic changes of anorexia nervosa. (129)

The reproductive consequences of suboptimal nutrition and/or altered body composition are usually reversible on refeeding. (125) Bates identified 47 women with either unexplained infertility, anovulation, or inadequate corpus luteum function on the basis of caloric restriction with reduced body fat. Eleven (23%) of the patients refused refeeding designed to increase their weight to a predicted ideal body weight complaining that it would make them

"fat." Seventy percent of those treated conceived spontaneously and 90% of women with secondary amenorrhea resumed menses. (127) There is no similarly complete information on nutrition and fertility in males.

Stress and Fecundity

Just as aspects of the biochemical environment can affect complex processes of reproduction, so can interactions with other environmental conditions cause bodily changes which can impair fecundity. This seems intuitively obvious. Even so, the relationships between "stress" (stimuli or conditions which perturb homeostasis and require adaptation) and impaired fecundity is extraordinarily difficult to prove in humans. This is most likely because each concept is difficult to define and both are greatly influenced and manifested by complexities of behavior.

Selye's original 1936 discussion of adaptation to stressors still forms the basis for understanding manifestations of stress: stressors challenge the homeostasis of the organism and the "adaption syndrome" is the manifestation of the body's "natural endeavor to maintain homeostasis." (130)

That psychological dimensions, as well as more mechanistically understood bodily processes such as heart rate and temperature regulation, are involved in whole body homeostasis is most clearly seen when the interrelatedness of reproductive processes is considered. Input from the limbic system and other brain centers affect the hypothalamus, hypophysis, and neurohormonal axis which orchestrates both the physical and behavioral aspects of reproduction. Darwin wrote of these relationships in 1868 noting that confined animals were "eminently liable to suffer in their reproductive systems." Given the power of these concepts and the frequency of human clinical infertility, it is not

surprising that in recent decades, 40-50% of infertility was attributed to stress or emotional factors. (131) Recent progress in neuroendocrinology and reproductive medicine has reduced this estimate to 5% or less. (131)

Critical reviews of the immense information regarding stress and fertility in different life forms are available. (132-136) Much research in this area is marked by lack of or misuse of controls and misinterpretation of epiphenomenon as causally linked results. In various animals, confinement, social stress, high altitude, surgery, and immobilization affect body weight, gonadal hormone levels, gamete maturation, reproductive organ morphology, fecundity and litter size, as well as copulatory and parental behavior. (134) Stress applied to the pregnant rat also affects the development and sexual behavior of male offspring. (131, 133) In humans, evidence suggests that mild to severe emotional stress alters sexual behavior and interferes with ovulation and depresses testosterone and perhaps interferes with spermatogenesis. (131, 134)

Certain information indicates that neurotransmitters play central roles in stress adaptation. It is further understood that neurotransmitter roles are not limited to effects on the central, peripheral, or autonomic nervous system functions but are also directly involved in reproductive tract physiology. (138) Understanding of increasingly unified and shared concepts of organ system physiology is growing rapidly. Yet, despite this information, great difficulties persist in accurately attributing individual cases of human infertility to stress or particular stressors, whether they are primarily physical or psychological. Much work remains as we define the variable processes of human reproductive adaptiveness. Most stress induced changes appear reversible.

Contraception and Fecundity

The possibility of sterility following use of contemporary contraceptives periodically causes great concern, usually because of overstated accounts of research, lawsuits filed, and simple misinformation. Nevertheless, because contraceptives are extensively used, especially by young individuals whose fecundity generally lies ahead of them, any significant morbidity is of concern.

Except for surgical sterilization, patterns of use of contraception among sexually active teenagers is similar to all U.S. reproductive age women (15-44 years) (138, 139). Overall, types of contraception used vary with age, marital status, reproductive history, and race. (139) Individuals and couples tend to change forms of contraception with time, need, and with public concern raised about one form as compared with others. Excluding sterilization, the most widely used methods of contraception in 1982 were birth control pills (16%), condoms (7%), diaphragm (5%), and the intrauterine device (4%). (139) About 2% of women used some form of periodic abstinence, withdrawal, douche, foam, and suppositories were used variously by similar small percentages of women. Importantly, only 51% of black women and 55% of white women were using any form of contraception, including sterilization, even though many were having intercourse without a desire for pregnancy. (139) Therefore, it is important to keep in mind relative risks and benefits of contraception versus those of unplanned pregnancy, childrearing, and abortion.

Many reports of adverse outcome ascribed to contraceptive use are anecdotal and do not compare outcomes in similar populations. It is clear that there are many causes of decreased fecundity which occur naturally. North American and European data suggest that in age determined maximally fertile populations, approximately 20-25% of couples conceive within one month

of unprotected intercourse, 66-70% conceive within 6 months, 80-90% in 12 months, and 90-95% within 24 months. (140, 141) Because the prevalence of infertility is up to 42.5% in some populations, great care in selection of control groups and statistical methodology is required. (140, 141)

The two largest, well controlled evaluations of nulligravid and parous women discontinuing oral contraceptives to become pregnant demonstrate very similar findings in vastly different parts of the world. (140, 142). Both demonstrate a small but significant initial impairment of fertility in nulligravid and parous women who discontinued pill use compared with other contraceptive methods. (140, 142) The magnitude of this relative decrease diminishes rapidly with time and is probably due to transient pill associated amenorrhea and anovulation. (140, 142) The Oxford Family Planning Association study demonstrated that differences in birth rates became negligible in nulliparous women by 30 months and in parous women by 42 months. In the parous group, only 3.5% of past pill users remained undelivered after 42 months, compared with 3.4% of other contraceptive users. Similar figures for nulligravidas were 10.7% and 9.4%. Vessey et al emphasize that this data relate mainly to women beginning pill use after age 20 and who used 50 ug estrogen preparations. (140) Other data from smaller or less adequately controlled studies confirm these findings. (143) As Stein emphasizes, these modest fecundity differentials primarily concern older women or couples with previously impaired fecundity. (30)

Progesterone only "minipills", which act primarily by inducing local genital tract alterations rather than inhibiting ovulation, are even less likely to impair fecundity than combination pills. (144) Data from several small series suggest there is little or no ovulatory suppression after discontinuing minipills. (143)

Much concern has been mounted about the delay in the return of fertility following the use of various injectable hormonal contraceptives. (145) Indeed, relatively prolonged absorption and hypothalamic-pituitary mediated anovulation is the basis of their action. There is clear evidence that ovulation and fertility return after injection of depo-medroxyprogesterone acetate which is designed to last 3 months (150 mg) or 6 months (300 mg). There is, however, a median delay in conception of 5.5 to 7 months after the term of complete contraceptive protection ends. (145) This is only 1-4 months longer than the median conception time following IUD discontinuation. (143, 145, 145). A number of other injectable contraceptive formulations are less well studied but do not appear to decrease fecundity after the medication is metabolized. (143, 145)

Estimates of the incidence of post-pill amenorrhea range between 0.2% to 2.7%. Disagreement persists as to whether this syndrome is specific to pill use, coincidental, or caused by use of birth control pills to suppress anovulatory menstrual bleeding originally. Harlap and others present evidence that women with post-pill anovulation may be divided into groups: one with otherwise unexplained anovulation and the other with some underlying factors, such as weight loss, prior oligomenorrhea, hyperprolactinemia or polycystic ovary disease. (147, 148) Post-pill amenorrhea in which no concomitant factors are found diminishes with time. Post-pill amenorrhea responds quickly to ovulation induction. (149)

A number of reports suggest that use of oral contraception provides some protective effect against pelvic inflammatory disease (PID). (150) Washington suggests that this proposed protective influence, possibly mediated by thickened cervical mucous, reduced menstrual bleeding, or altered endometrial lining, is more apparent for gonorrhea rather than chlamydia associated pelvic inflammatory disease. (151)

Use of intrauterine devices (IUDs) has caused the most concern in regards to fecundity. Much historical and anecdotal information, as well as a number of variously designed epidemiologic studies, strongly suggest that wearing an IUD predisposes to pelvic inflammatory disease. (150, 152) Many of these studies, however, do not demonstrate statistically significant differences, and none carefully examined other, possible confounding, risk factors, which put women at risk for PID. Nevertheless, similar findings from diverse sources, are generally consistent, and "are probably real." (150) Increased risks of IUD-associated PID are most strongly linked in users who are young and nulliparous. (150) Despite linkage with pelvic inflammatory disease, impaired fecundity after IUD use is not apparent when cumulative conception rates of large numbers of predominantly married, middle class women are followed prospectively. (140, 153) Daling noted that data on IUD use and infertility "falls short of being conclusive." (152) Subsequently, groups lead by Daling and Cramer clarified these issues in differently designed case"control studies of women with tubal infertility. (152, 154)

Daling and colleagues determined the risk of primary tubal infertility in women (159) who had ever used an IUD was 2.6 times that of women who have never used one. (95% confidence interval 1.3 to 5.2)(152) Dalkon Shield use was significantly associated with tubal infertility. Use of other plastic IUDs was associated with tubal infertility (relative-risk 3.2 with 95% confidence intervals of 0.9 to 12.0) but not significantly. Copper-containing IUD users had a lower increased risk (relative risk 1.8, confidence intervals 0.9 to 4.0). Studying a greater number of women with primary infertility, Cramer and co-workers demonstrated overall lower relative risks of tubal infertility for each type of IUD, but differences were more frequently significant. (154) They further noted that (1) women who reported only one

sexual partner suffered no increased risks of tubal infertility associated with IUD use; and, (2) risk of secondary tubal infertility was not significantly associated with copper-containing IUD use. (154) This information reinforced the clinical concept that IUD use was most appropriate for women who had completed their families. Discussions of relative risks versus benefits of IUD use have been preempted, however, by the withdrawal of all but one type of IUD from U.S. markets. Otherwise, IUD use continues worldwide in the light of accumulated understanding.

Use of other effective forms of contraception are not linked to any specific fecundity impairment, beyond that associated with aging. Barrier forms of contraception may reduce risks of development of sexually transmitted diseases which mediate acute salpingitis and subsequent tubal infertility. Prevention of sperm antibodies in women has also been hypothesized as a benefit of barrier contraceptives or withdrawal. Effects on subsequent fecundity caused by use of newer agents, such as progesterone antagonists RU 486, remain unstudied. (155)

Abortion and Infertility

Demographic information suggests that there are approximately 90 million births worldwide each year and 40-50 million abortions. (151) Thus, induced abortion, with its risks and sequelae, has become one of the most widely used forms of fertility control.

As with birth itself, pregnancy termination is associated with complications, including possible impaired fecundity. The impact of induced abortion on subsequent fecundity in comparison with various controls has been extensively studied, analyzed, and subjected to a standardized critique. (156-162) With the exception of a study from Greece (143), where abortion is

illegal, no studies of dilatation and curettage or vacuum aspiration abortion reliably demonstrate measured impaired fecundity following abortion. (159) Indeed, two studies report significantly shortened interpregnancy intervals following abortion. (163, 164) These findings are most probably explained, however, by particular patient characteristics rather than any enhanced fertility due to abortion.

Unlike a number of similar negative studies, Daling and co-workers demonstrated a statistically insignificant relative risk of 1.2 for tubal infertility subsequent to abortion. (165) The authors ascribed this arithmetical increased risk to sequelae of pelvic inflammatory disease after abortion. Risk factors for pelvic inflammatory disease (PID) following abortion include: (1) prior history of PID; and, (2) cervical infection with Chlamydia trachomatis and Neisseria gonorrhoeae. (166, 167) These studies strongly suggest that these two infections be identified and treated before or coincident or shortly after abortion. (166, 168) A prior history of PID should be determined, and patients who are identified prophylactically treated with a short course of antimicrobials active against lower genital tract mixed anaerobic-aerobic microflora (i.e., Doxycycline 100 mg twice daily for 3 days, Ampicillin or Augmentin 500 mg four times daily orally for 3 days, or Metronidazole 500 mg twice daily for 3 days). (168) Surgical care during the procedure is likely more important in preventing subsequent infection than is antibiotic use.

Studies of fecundity following second trimester evacuations are small and inconclusive regarding risks of subsequent infertility. Prophylactic antimicrobials are commonly given if the procedure takes longer than 24 hours to complete.

Genetic and Chromosomal Abnormalities and Fecundity

In most animals, including man, reduced fecundity or sterility due to genetic or chromosomal disorders is well described. (169, 170) Indeed, the discovery of chromosomal abnormalities in laboratory or domestic animals is often prompted by decreased fertility. Research in humans, rodents, Drosophila, and many other species illustrates the nature and extent to which reproductive, especially gonadal, functions are impaired by genetic or chromosomal abnormalities. The subject is complex and recent reviews should be consulted for detailed considerations. (169) Interestingly, in most species examined, infertility on a chromosomal basis predominates in males. This pattern is found in surveys of infertility clinics as well. In one large survey of infertile couples, over 2% of all men possessed abnormal karyotypes. (170) This was three times higher than the rate of chromosomal abnormality found in newborns of the same population. When azoospermic men were analyzed, fully 15% possessed abnormal chromosomes. (170) Women with XO, XY, and various mosaicisms (XO/XX, XO/XY, XO/XXX, etc) and other abnormalities are sub-fecund or sterile.

Preventive impaired fecundity in progeny is, to some extent, carried out naturally as the majority (50-60%) of early pregnancy losses appear to be chromosomally abnormal. Recent work by Wramsby and colleagues shows that approximately 50% of unfertilized oocytes obtained from clomiphene stimulated ovaries of infertile women are chromazomaly abnormal. (171) Prior studies demonstrate that approximately 9% of spermatazoa from normal males possess abnormal chromoszomes. (172) In a unique study, Hertig and Rock in 1945 reported on 107 patients who had timed intercourse prior to hysterectomy over a twenty year period. They observed that approximately a third of these unimplanted or early implantation conceptuses were

morphologically abnormal. (173) Such structural abnormalities have been presumed to be linked with chromozomal abnormalities. (ed NJM) When all factors are taken together, estimated reproductive losses before women are know to be pregnant approximate fully 60% of conceptions. (174, 175) The extent of this "natural" or "background" rate of early reproductive loss, and our continuing ignorance as to its causes needs to be acknowledged. Reproductive losses occur before pregnancy can be recognized, and can be incorrectly accounted as "infertility". Given our limited knowledge regarding the "black box" of human conception, fallopian tubal transport, implantation and early growth, nothing can be scientically done to prevent reproductive wastage very early in pregnancy.

Future medical reduction of impaired fecundity due to genetic factors depends upon detection of genetic abnormalities in early pregnancy. Genomic treatments may be possible in the future, but at present, preservation of a couple's fecundity in which one or both partner's reproductive capacity is impaired is best treated by expeditiously supplying alternative means of conception.

Cystic Fibrosis

Cystic fibrosis is the most common severe inherited disease of caucasians with an incidence of 1 in 1600 to 1 in 2000 individuals. (176) The major complications of this autosomal recessive disease are intestinal malabsorption and recurrent bacterial pulmonary infection associated with progressive lung disease. In earlier decades, most affected individuals died before reaching reproductive potential. With contemporary multisystem supportive care, a median of cystic fibrosis patients survive to age 19. This trend is expected

to continue allowing many more patients to survive into reproductive age groups. As many surviving patients are interested in establishing families, issues surrounding fecundity have become of special concern.

Puberty is commonly delayed in cystic fibrosis patients and the degree of delay correlates primarily with severity of illness and height-weight ratios. (176) Although pulmonary disease of any origin can restrict sexual performance, the majority of couples in which one partner has cystic fibrosis have "successful sexual relationships." (177)

The vast majority of male patients are azoospermic on the basis of incompletely understood ductal defects. (176) After genetic counseling, semen analysis may be done in males who wish to reproduce. If spermatozoa are recovered, then collection and cryopreservation may be considered to allow enhancement of elective conception in the future.

Fertility and fecundity in women patients appear anecdotally reduced. Menstrual abnormalities, probably mediated by the presence of ongoing illness, occur in roughly half of these women. Various abnormalities of cervical mucous are described which may interfere with sperm transport. Fecundity can be enhanced by careful counselling on how to improve chances for conception and possibly by artificial insemination. The appropriateness of any pregnancy in a couple afflicted with cystic fibrosis should be most carefully considered, given current inability to correct the underlying metabolic deficiency and to satisfactorily identify affected conceptions. Although pregnancy does not provably increase maternal mortality, such pregnancies are frequently complicated and parenteral survival will inevitably be limited in any case. (176)

Immunological Infertility

An enthusiastic case can be made suggesting that heightened levels of various antibodies toward sperm or seminal fluid antigens in either men or women may be associated with otherwise unexplained infertility. (154) Since normally fertile men and women frequently posses such antibodies, it has been suggested that these immunoglobins play physiologic roles in absorbing or clearing senescent spermatazoa. (154) Development of such antibodies is not understood. It is theorized that genetic predispositions (as determined by histocompatibility antigens), violation of blood-testis barriers subsequent to trama, surgery, or possibly bacterial or viral infections involving the testes, epididymis, or vas deferens may bring about autoimmunological reactions in males. (154) These infections may include chlamydia, Mycoplasma, other bacteria commonly involved in male genital tract infection, as well as viral causes of orchitis. It is presumed that women develope antibodies to sperm and/or seminal plasma antigens during intercourse. Details of the specific stimuli and time course in developing such antibodies remain unstudied.

Despite enthusiasm for greater recognition of immunologic infertility, controversies over methodologies and antigenic systems present on spermatozoa and in seminal plasma make immunologic infertility an unsettled area. (178,179) Postponement of intercourse, restriction of numbers of sexual partners, and consistent use of barrier contraceptives seem to be reasonable, but speculative, preventive strategies against development of anti-spermatozoa and anti-seminual fluid protein antibodies.

Fecundity Preservation and Procreative Alternatives in Cancer Patients

Transient or permanent gonadal damage and dysfunction may occur during cancer therapy with surgery, radiation, and chemotherapy. Evaluations of the occurrence, types, mechanisms, and means to prevent both possible gonadal disease and genetic damage are important. Increasing numbers of young, potentially fertile individuals continue to benefit from improved understanding and treatment of many neoplasms. (180-183) Research suggests that the effects of various antineoplastic treatments are affected by age, total drug or radiation dose, duration of treatment, use of single agents versus multiple agents or combined modalities, and length of time since cessation of treatment. (183, 184) Estimates of radiation doses causing sterility in men and women is displayed in Table 5. (185, 186) Classification of various chemotherapeutic risk for male germ cell depletion is presented in Table 6.

Overall, alkylating agents and combination treatments for Hodgkin's disease treatment are most damaging. Precise information on thresholds of gonadal vulnerability and ability to recover is not available. There is scant information on threshold doses for radiation and/or chemotherapy induced gonadal dysfunction and the influence of pubertal status remains controversial. (183, 184)

Cancer treatment ovarian damage includes hormonal alterations, reductions or obliteration of oocytes and fibrosis and failure. Ovarian failure in these circumstances is age-related with older women being predisposed to sterility at lower dose regimens. (183) Oophoropexy with pretreatment movement of the ovaries outside of the anticipated radiation field (either adjacent to the iliac crest or immediately behind the uterus) is useful in decreasing ovarian exposure during radiotherapy. Oophoropexy can be

done in conjunction with staging procedures for Hodgkin's disease and various lymphomas. Schemes to preserve ovarian and testicular function and potential during chemotherapy are based on suppression of the hypothalamic-pituitary-gonadal axis with gonadotropin curtailing doses of estrogen-progesterone (birth control pills) combinations or gonadotropin releasing hormone (Gn-RH) analogs. (187) Based on these approaches, a number of agents are undergoing evaluations as means of preserving gonadal function and thus fecundity during cancer treatment.

In cases where there is a significant chance of sterility subsequent to cancer therapy, steps may be taken to provide appropriate patients with information concerning presently practicable procreative alternatives. Although sometimes considered "unnatural", collection of sperm or oocytes from potentially curable cancer patients has much appeal and is not necessarily expensive in relation to other therapeutic costs. Semen collections with sperm banking using liquid nitrogen cryopreservation is well established, relatively uncomplicated, inexpensive, and effective in achieving subsequent pregnancy by artificial insemination or in vitro fertilization years after collection. (188)

Superovulation and collection and cryopreservation of female egg cells is also increasingly practicable and can grant otherwise impossible to provide ability to have a family for some women. Prospects for preservation of female and male fertility in the face of cancer therapy will likely increase greatly in the near future as presently available techniques are more widely employed and new ones are developed.

Reproductive Tract Cancers

Obviously, fecundity will be impaired if there is direct damage or therapeutic extirpation of female or male genital tract structures required for procreation. Cervical, uterine or endometrial, ovarian and testicular neoplasia are not uncommon. These and other tumors are clearly best prevented entirely or treated in precursor stage. Treatment either early or late in the course of various genital tract neoplasia commonly requires organ removal and may not prevent loss of reproductive function or guarantee survival. Cancer of the cervix, uterus, and to a lesser extent ovarian carcinoma are associated with certain risk factors involving "life style", possible specific oncogenic exposures, and inherited predispositions. (189) Cervical, and to a lesser extent, vaginal and vulvar carcinoma have been associated with increased number of sexual partners and the increased occurrence of sexually transmitted disease. Although inconclusive, present information strongly suggests that much of this predisposition is accounted for by infection with specific serotypes of human papilloma virus (HPV) infection. Specific prevention, identification, and treatment of human papilloma virus infection may offer important strategies to prevent certain lower genital tract squamous cell carcinoma and adenocarcinoma. Recommendations for lower genital tract cancer screening include pelvic examination and pap smear beginning after the onset of intercourse and repeated at least every three years after two negative examinations. Women at higher risk on the basis of HPV or prior herpes simplex virus infection should be evaluated yearly. (189) Women at risk for vaginal or cervical clear cell carcinoma on the basis of intrauterine exposure to DES require more frequent specialized examinations, including careful vaginal palpation and vaginal smear and/or colposcopy.

Development of endometrial carcinoma is associated with a history of sustained high fat diet and prolonged periods of anovulation or relative infertility. Preventive stratagems include periodic progesterone or progestin induced endometrial shedding and prompt histologic evaluation of otherwise unexplained abnormal uterine bleeding. Histologic sampling of endometrial tissue may be performed on a periodic basis in perimenopausal women or women with prolonged anovulation from whatever cause. (189) Some ovarian carcinomas may occur on a familial basis. In addition, relative infertility and relatively increased ovulation without pregnancy appear to be risk factors for ovarian carcinoma. Use of talc containing hygienic products has also been proposed as a preventable cause of ovarian cancer. Detection of ovarian carcinoma before it reaches an advanced stage is difficult. It is possible that increased use of advanced ultrasound, prominently with intravaginal probes, will allow improved surveillance for ovarian neoplasia in women selected on the basis of history of ovarian neoplasia in close relative or in women who possess a "Y" chromosome. Programs have been mounted urging that self and professional testicular examination be done on a regular basis.

Recommendations for treatment of genital tract neoplasia will likely be revised frequently in the future as more information on the biological basis and natural history of reproductive tract cancer is elucidated. Much of this information will likely be useful in preserving fecundity.

Non-Therapeutic Radiation and Fecundity

Knowledge of the effects of various types of radiation on human fertility is derived primarily from studies of male and female Japanese atomic bomb survivors and populations exposed to increased levels of natural radiation.

(190) These studies disclose no significant relation between radiation exposure and measures of fertility and fecundity. (190) A retrospective study wasperformed by Polednak of 199 women exposed to internal and external radiation while employed in the radium watch-dial painting between 1916 and 1929. Multiple regression analysis demonstrates radiation of mean log live-birth rate in women who received the highest estimated ovarian dose (20 rem) versus women who received the lowest estimated doses (5 rem). No other reproductive abnormalities were described. (190) Because many attributes, such as contraception, of these women were not available, Polednak concluded that "these data must be interpreted with caution". (190) Similarly well delineated large studies of male non-therapeutic radiates exposure are not yet available.

So far, these data suggest that statistically significant measures of decreased fecundity in individuals exposed to radiation is difficult to demonstrate and that it is only individuals subject to accidental or industrial exposures who are at measurable risk. There is scant information on the larger question on the effects of natural and non-natural radiation on human germ cells of populations exposed to various types and amounts of radiation in men and women.

Environmental and Drug-Induced Decreased Fecundity

Until relatively recently, little attention has been paid to environmental and drug-induced infertility and sub-fecundity. Astonishingly, a recent review of work on environmental "health risks" omits mention of reproduction. (191) Part of this relative neglect originates from the

complexity and uncertainty of reproductive function and outcome. Considerable recent efforts in developing appropriate methodologies for surveillance of environmental or drug altered fecundity are crucial to further progress. (192, 193)

Given the difficulty in measuring fecundity alterations in human populations, development of *in vitro* and animal models test systems are necessary for screening and establishing pathogenic mechanisms in newly developed substances. Monitoring of humans at risk from specific substances is necessary since toxic effects are frequently species specific. Because possibly toxic agents vary in importance and in how much is known about them, only a few substances will be selectively discussed. Agents considered to interfere with male or female fertility are presented in Table 7. (194-196) It must be remembered that many more agents are associated with poor reproductive outcomes (teratogenicity, growth retardation, etc.) than are demonstrated to cause infertility.

Glycol ethers are the best studied of reproductive toxins. (197) This important and widely used class of solvents are embryotoxic and teratogenic in male and female animals and produce testicular atrophy and infertility in male animals. Results are consistent across various species. (197) Nevertheless, reproductive toxicity remains to be demonstrated in humans. This reinforces criticism of simple case reporting relied upon in the past.

Medications and substances used for self intoxication which interfere with fertility are noted in Table 8. Most prominent among these agents are cigarette smoking, chronic and acute alcohol consumption, and cannabis smoking. *In utero* exposure to DES is associated with abnormal reproductive development in males and females when they mature. While development of

vaginal adenocarcinoma in women is rare, it can cause mortality as well as infertility. Reports suggest that males exposed to DES commonly have abnormal spermatozoa and potentially diminished fecundity. (198) The effects of physical forces on fertility are shown in Table 9. (199)

Smoking

Rapidly increasing research demonstrates that smoking impairs performance of males and females in nearly each phase of reproduction from "gametogenesis to implantation" and beyond. (200-202) Variously designed epidemiologic studies from different countries confirm an association with smoking and infertility and menstrual abnormalities in women. (201, 203) Smoking appears to shorten potential reproductive life span by decreasing the age of menopause in a dose-related way. (204) The effect of smoking on male fertility is less well established but smoking or nicotine consumption is associated with decreased spermatozoa numbers and increased numbers of abnormal forms in rodents and men. (200) Experimental finding suggest that these alterations are caused by changes in hypothalamic-pituitary axis function and possibly by impaired motility of cilia in the genital tract. (202)

While alcohol consumption impairs fecundity in laboratory animals by a variety of mechanisms, human infertility from "moderate" non-habitual alcohol consumption is not apparent (203) Chronic alcohol abuse is consistently associated with abnormalities of spermatogenesis and presumed sub-fecundity in males.

Both smoking and alcoholic and other abused substances interfere with embryogenesis, intrauterine development, growth, and health of conceived children in a variety of important ways. (200) Strong arguments are made for prohibition of these substances in couples attempting to conceive and in those who are pregnant or lactating.

Surgery and Fecundity

Intraabdominal pathology and surgical procedures can impair a woman's fecundity primarily by producing fallopian tube or ovarian adhesions. Much information links appendicitis and appendectomy, and other pelvic operations with tubal-based infertility. (45,205) Tubal damage from ruptured appendicitis and other causes of pelvic peritonitis and pelvic abscesses may occur in childhood and not be recognized until pregnancy is desired. (204) Mueller and Daling found a 4.9 fold increased risk of tubal infertility after surgery for patients reported with "ruptured appendectomy." (205) They calculate that approximately 5% of tubal infertility is due to ruptured appendices. (205) While this is not a large percentage overall, the damage may be preventable by timely surgery and recognition of the possible influences of "surgical" infection on eventual reproductive potential. Similarly, any surgery or pelvic structure may cause adhesions and positive steps should be routinely taken to reduce the possibility of postopertive scarring. Scientific study of prevention of tubal and ovarian adhesions will further aid in preservation of fecundity in women who require pelvic surgery (207, 208).

Pelvic and reproductive reconstructive surgery should be done in a timely way which maximize reproductive potential. As noted, surgery to correct imperforate hymen or other causes of menstrual fluid outlet should be completed before onset of menses to reduce the risk of endometriosis. (209).

Corrective surgery (orchiopexy) for maldescended testes (cryptorchidism) appears necessary in the first few years of life to prevent infertility or sterility as well as to avoid tumor development in intraabdominal testes. (210, 211) Correction of left varicocele at puberty is propsed as a means to prevent male subfertility. (212) Reconstructive surgery of major genitourinary deformities such as extrophy can allow reproduction in survivors. (213)

Sterilization and Fecundity

Surgical sterilization of males and females is the most common form of birth control used in older age groups. (7) Despite preoperative counselling, approximately 0.5-1% of all sterilized individuals request reversal so that fecundity can be restored. (214) With fallopian tube occlusion, the surgical method, tubal site, length of tube remaining and time between sterilization and reveral, and surgical skill in restoration, are all important factors in determining restoration of fecundity. (214) Boecky notes up to 92% conception rates if isthmo-isthmic reanastomosis is accomplished with tubal length of at least 4 cm. (215) Unfortunately, isthmic tubal resection is associated with heightened risk of failure of sterilization in women. Factors which are most important in male sterilization reversal are time since sterilization and surgical technique used. (214)

The frequency of requests for sterilization reversal appears linked to the popularity of these methods and the occurance of changed family circumstances. (214) Ideally, counselling should reduce poststerilization regret and requests for reversal.

Inflammatory Bowel Disease

Ulcerative colitis and Crohn's disease occur most frequently in reproductive age individuals with approximately equal frequency among the sexes. (216-218) Ulcerative colitis does not appear to impair fecundity. (216) On the other hand, the preponderance of reports suggest that Crohn's disease is associated with diminished fertility and fecundity in men and women; causes are not well established. The bowel disease may spread and develop within reproductive tract tissues, especially the fallopian tubes, or it may secondarily lead to tubal adhesions. Medical advice to avoid pregnancy or disease induced debility or uncomfortable coitus may reduce coital frequency. (217) Men and women with active disease may experience impaired fertility due to poorly understood "constitutional" mechanisms operating in acute or chronic illnesses.

Analysis of reported series shows that conception occurs when disease is inactive or mild and that surgical treatment is associated with higher fertility. (216-218) Corticosteroids and sulfasalazine do not influence female fertility. However, sulfasalizine is occasionally associated with impaired spermicogensis which is reversed 3-4 months after discontinuing the drug. (216, 217)

Overall, fertility in women with Crohn's disease can be optimized by successful medical and surgical control and by attempting pregnancy when the disease is quiescent. Males taking sulfasalozine should have semen analysis if pregnancy is desired.

Miscellaneous and Unexplained

Preventable causes of subfecundity not yet discussed include cervical damage subsequent to removal of endocervical tissue in the course treatment for cervical cancer precursors (219). Oophoritis and orchitis due to mumps and other preventable infections appear less common as mumps vaccination is nearly universal in the U.S. (220). Other causes of gonadal failure are diverse and not easily preventable (221).

In approximately 10-20% of infertile couples, no clinically apparent cause of infertility is demonstrable using standard techniques. (222-224) It is likely that many couples with unexplained infertility actually suffer from subclinical expression of acknowledged causes of infertility which can be revealed by further testing or continued observations. Wood performed laparoscopy on 50 women whose basic couple evaluations were normal. (226) Fully 28 (56%) demonstrated either previously unsuspected peritubal adhesions or endometriosis. Of those who had abnormal findings, 16 received appropriate treatment and 50% became pregnant within a year of treatment versus 10% in the women who had no abnormalities. (226)

For couples whose infertility stems from subclinical adhesions and endometriosis, stratagems aimed at prevention of these problems may have been of help in preventing or ameliorating these processes. Other consistently mentioned candidates for causes of unexplained infertility

include ovum entrapment, deficient spermatozoa fertilizing capacity, as well as numerous immunological abnormalities. (222) Given time, couples with unexplained infertility do not fare badly. They achieve at least one pregnancy with up to 87% by 5 years. (227)

It is remarkable that there is so little "unexplained infertility" considering the great intricacy of the molecular interplay which must occur for conception to occur. New realms of physiologic understanding are opening: some of the most promising involve prostaglandins and related substances pheromones. Increased understanding in each of these areas will yield new opportunities for prevention as well as treatment. Some other couples reproductive potential may be improved by artificial insemination or external fertilization. (228)

Continued research into basic reproductive development and physiology and how these processes may go awry is crucial. Other important areas of study include political, social, economic, and cultural factors which can act to impair an individual's fecundity by influencing reproductive behavior and/or adversly affecting biologic reproductive potential. Scientific studies of these influences on fecunditiy are just begining. A recent analysis of political, sociologic and demographic aspects of fertility in China demonstrates the necessity of multidisciplinary approaches towards understanding the dynamics of human reproduction (as well as, social policys which seek to "manage" reproduction). (225)

Obviously, preservation of fecundity in the face of unrecognized problems is problematic. If a couple's need to conceive is an overriding concern, then attempts at pregnancy should be initiated as promptly as possible and sustained.

Synthesis

Precise classification and ordering of importance of the causes of infertility remains problematic for several reasons. Diagnostic techniques are commonly inaccurate. Discrepant results between clinical findings and results of laproscopy are as high as 44%. (M, 1982) Classification of infertility due to any one cause is often arbitrary and misleading. "Causes" of infertility involving one or both members of an infertile couple are often multiple. Multiple eticlogic factors may interact in ways which can not be easily measured, but must be individually treated. (Vevauf, 1983) (23) Indeed, it may be the combination of factors which decisively impairs fertility rather than any one single factor (which does not itself cause sterility). For instance, if a man with oigospermia marries a woman with partially obstructed fallopian tubes the couple is likely to be infertile. On the other hand, if either had married fully fertile individuals, then fertility would be much more likely. Differences in locale, type of patients being reported (age, time attempting pregnancy, race etc), and completeness of evaluations make comparison of reported series uncertain. Further, reported clinical compilations of infertile patients do not include individuals and couples with obvious causes of sterility (such as prior sterilization, castration, or hysterectomy) and those who do not or can not present for evaluation.

Acknowledging these considerable methodologic difficulties, a listing of factors ascribed as primary causes of infertility in three large, (1141 total couples) recent U.S. studies of infertile couples is presented in table 10. Since diagnostic criteria are not entirely uniform, grouping are by general category in order of clinical importance. Estimation of how many couples at 30 years of age might present with each ascribed cause of infertility is

made. Comment is given on the possibility of preventing such causes of infertility and a judgment is given of the likelihood of a general acceptance of specific preventative measures (table 10).

Conclusions

"Sex hygiene is today a fetish, bandied about by the pedagog, the preacher, the politician and the physician in the endeavor to escape the responsibility of indicating the application of the subject to a practical science in education. Congresses debate some phases of sex hygiene; both sides are vehement in urging and opposing the dissemination of knowledge among the young, and while they continue to disagree, the young go on learning in the old-fashioned way.

Dyer I: Sex hygiene. Am J Public Health 6:293, 1916

Development and implementation of effective and safe preventive strategies depends upon thorough understanding of the problem. While much is known about maintaining fecundity, vast gaps in knowledge impede further progress. The immediate needs for research and further understanding include:

1. Fuller realization and broadened inquiries into all aspects of reproduction, including sexuality. Reluctance to scrutinize such basic human characteristics and behaviors retards and distorts our abilities to deal with the realities of reproduction as individuals and or a society.

2. More complete epidemiologic definitition and analysis of decreased fecundity. Present knowledge derives from relatively small geographically and

ethically limited surveys and case reviews. Development of methodogic techniques and uniform terminology will be crucial for measuring all aspects of fertility and communicating the results.

3. Fuller understanding of social and economic aspects of fertility for individuals, women, men, families, and society at large. Integration of careers and reproduction remains poorly studied in U.S. populations.

4. Enquiries into both normal and abnormal male and female reproductive physiology must proceed with full societal support. Rudimentary questions remain unasked, much less answered. How does aging reduce fecundity? How do body mass and composition, as well as exercise and "stress", influence reproductive ability? Solutions to these and other solvable questions would offer means to prevent these causes of physiologic subfecundity.

5. Specific disease-oriented basic and clinical research, which can lead to dramatic advances in prevention. Development of vaccines against various infectious diseases has been crucial to their control. Vaccine development for STDs, including Neisseria gonorrhoeae and Chlamydia trachomatis is difficult because of incomplete understanding of each organism's molecular biology, virulence, and means to induce protective response in human hosts. With time and sustained supported effort, these difficulties can be overcome. In the meantime, new approaches to STD avoidance, detection, and treatment should be evaluated. As noted, male responses to genital tract infections remains virtually unstudied with modern methods. Similarly, little is known about the pathogenesis or prevention of endometriosis. This common discorder remains a disease of "hypotheses".

6. Research into how to most effectively communicate health-related information to general populations and selected groups remains rudimentary.

Current information is "trickled down" as "news" from various media or is dispensed piecemeal by care providers, and possibly parents and others. Initial attempts at using dynamic mass communication techniques for STD education are promising. (229) Doubtless, the exigencies of dealing with acquired immunodeficiency syndrome (AIDS) will greatly expand and refine effective use of mass communication for motivating health related behavior. On the other hand, there are limits to the simple application of information for affecting behavior. (230, 231) Further, preliminary information suggests that individuals at greatest risk for PID may be resistant to conventionally given cautions. (232) In this pilot study women with PID appeared more likely to: 1) Take health risks; 2) believe in luck; 3) be more socially alienated; endure symptoms longer; 7) and have coitus with a greater number of partners. (232) Effective advocacy of and other reproductive issues will require development of sophisticated and focused health education techniques appropriate for our pluralistic society. Imperitives of AIDS education and behavior modification will likely push frontiers of health-related education far further and faster than ever anticipated.

There is no need to wait for these and other lines of inquiries to bear fruit. Identification of the primary causes of impaired fecundity allows for specific medically'based proposals to be made. (233, 234) The most important of these are outlined in Table 11. Certainly, a strong medically-based case can be made against early onset of intercourse, especially for females. (235, 236)

Societal factors and forces promoting reproductive health and preservation of fertility require support. Teaching of health education in

schools and other organizationsmust appropriately provide reliable information on all aspects of reproduction, including sexuality and means to preserve fecundity. (237, 238) Since education regarding sexual matters can be controversial and goal-orients (reduction of teenage pregnancy and STDs), specially developed programs may be most effective. (239, 240) "Special" "remedial" sex and STD educational efforts should also be required for health care providers. Professional education in these areas is woefully inadequate. Importantly, lay manuals are often excellent, especially when devoted to the interests of specific groups. (241) Legal compulsions against transmission of STDs and possible loss of fertility will grow as the number of suits filed in cases of alledged infection increases. (242)

Less specific, and possibly more useful, preceptions of preventive reproductive care are psychologically and politically based. These depend upon the assumption of worth for each individual. If care providers and others, including parents and educators, presume the value of each individual, then health-related information, including understanding of the risks and rewards of sexuality and reproduction, will naturally be given. Even better yet, if the individual values him or herself then they will be self-motivate to acquire information necessary to understand and protect themselves throughout life.

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Table 1. Reproductive terms regarding fertility (7).

Fecundity: The physical ability of a woman or a couple to reproduce as determined by asking simple questions

Categories:
1) Fecund: able to reproduce freely
2) Impaired fecundity: Not able to reproduce freely
3) Surgically sterile:
   (a) contraceptively sterile
   (b) non'contraceptively sterile

Infertility: A medical concept identifying couples that may need medical services to improve their chance of having children. When neither partner is surgically sterile, a couple is considered fertile if, during the previous 12 months orlonger, they had continuous opportunities for intercourse and did not conceive.

Categories:
(1) Fecund: Neither surgically sterile or infertile and physically able
(2) Surgically sterile
(3) Fecund: Everyone else, who is neither surgically sterile nor physically able

*Measures of infertility generally provide lower estimates than impaired fecundity since this category includes only wives or couples who have difficulty conceiving and excluding those who are using contraception because of pregnancy would threaten their health.

Table 2. Diagnosis of couples seen for infertility in different regions ofthe world. (U.S. data resemble those of other developed countries) (After Cates W Jr: Worldwide patterns of infertility: Is Africa different? Lancet ii:596-598, 1985)*

	PERCENTAGES		
	Developed Countries	Africa	Asia
Female diagnosis			
No demonstrable cause	40	16	31
Bilateral tubal occlusion	11	49	14
Adhesions	13	24	13
Acquired tubal abnormality	12	12	12
Anovulation	19	17	16
Oligomenorrhea	7	4	11
Hyperprolactinemia	7	5	7
Endometriosis	6	1	10
Male diagnosis			
No demonstrable cause	49	46	58
Varicocele	11	20	10
Primary testicular failure	10	7	11
Infection	7	11	3
Primary abnormal sperm	11	6	8

*Percentages do not add up to 100 because both members of couples were evaluated according to WHO criteria and diagnosis made independently.

Table 3. Categories of prevention measures for STDs (26).

Category of Activity	Level of Prevention	Example
Health promotion	Primary	Health education discourages casual sex encounters.
Health promotion	Primary	Local media campaign encourages condom use.
Health promotion	Primary and secondary	Television spots encourage men and women with genital discharge to be checked for STD.
Health promotion	Tertiary	Changes in societal attitudes towards venereal disease and childbearing lessen stigma for infertility due to STD.
Specific protection	Primary	Individual uses condoms to reduce risk of acquisition of an STD.
Early diagnosis and treatment	Primary	Screening and treatment program reduces future transmission from that group.
Early diagnosis and treatment	Secondary	Early detection and treatment of infection in contacts reduces rate of complications among them.
Disability limitation	Secondary	Rapid, adequate management of acute salpingitis and herpes virus infection reduces central nervous system sequelae or epididymitis-orchitis reduces risk of
Infertility Rehabilitation	Tertiary	In vitro fertilization and subsequent implantation compensate for fallopian tube obstruction due to complication of an STD.

Table 4. Calculated cumulative rate of post-salpingitis infertility in a hypothetical cohort of 100,000 Swedish women born in 1950 (209).

Birthday	Cummulative Number Infertile From Salpingitis
20th	869 (0.8%)
25th	1656 (1.6%)
30th	2431 (2.4%)
35th	2689 (2.7%)

* 2.4% (salpingitis induced tubal infertility) is approximately 30-40% of an expected 8% infertility rate. This percentage matches the proportion of infertility ascribed to tubal damage in various studies of infertile couples.

Table 5. General radiation doses estimated to cause sterility in 5% and 50% of women.

Reference	5% Sterility	50% Sterility
WOMEN:		
Lushbaugh, 1972	650 rads	2000 rads
Rubin, 1972	200-300 rad	625-1200 rads
MEN:		
Lushbaugh, 1972	450 rads	600 rads
Rubin, 1972	500-1500 rads	2000 rads

Table 6. Schilsky and colleagues estimates of antitumor chemotherapeutic agents risk for testicular germ cell depletions. Estimate refers to presumed standard doses. Agents given in combination may have less predictable effects. Age, gender, duration of treatment, and time since cesation of treatment also affect outcome. (Schilsky, 1982)

Degree of Risk	Agent
Definite	Chlorambucil, Procarbazine, Busulfan, Cyclophosphamide, Nitrogen Mustard
Probable	Doxorubicin, Vinblastine, Cytocine Arabinoside
Unlikely	Methotrexate, 5-Fluorouracil, 6-Mercaptopurine

Table 7. Chemicals established to affect female reproductive cycling and fertility. (After Heinrick WL: Reproductive hazards of workplace and home. Clin Obstet Gynecol 26:429-437, 1983)

Agent	Effect
Lead	Amenorrhea
Organochlorinated pesticides DDT Dieldren kepone	Uterotrophic (like DES), causes infertility with (chronic estrus) in rodents exposed postnatally.
Polychlorinated biphenyls (isulators, plasticisors)	(Same as above)
Ethylene dibromide	Occupational inhalation (0.5-5 ppm) in air causes infertility.

Table 8. Drugs or commonly used substances which can impair male fertility. (After Smith 1987, Beely 1984, Heinrick 1983)

Primary Site of Action or Use	Examples
1. Central nervous system tricyclic antidepressants phenothiazine narcotics	Tricyclic antidepressants, phenothiazine, benzodiazepines, marijuana, alcohol, nicotine, opiates
2. Autonomic nervous system (act by causing impotence)	Methyldopa, clonidine, beta blockers, anticholnergies
3. Chemotherapeutic	Most, see cancer section.
4. Inhibitors of synthesis, transport or action of sex steroids or spermatogenesis	Marijuana derivatives, phencyclidine (PCP), alcohol, Ketoconizole, cimetidine, estrogen in men. Sulphasalazine, tetrahydrocannabinol.

Table 9. Summary of effects of physical forces on fertility (derived from summary by Council on Scientific Affairs, Effects of Physical Forces on the Reproductive Cycle. JAMA 251:247-250, 1984)

Condition	Comment
Atmospheric pressure	
Low (high altitude)	Lower human birth rate
High (scuba diving)	No data
Electric and magnetic fields (many sources)	No adverse effects noted
Gravity and acceleration	No adverse effects noted
Hyperthermia	Reversible damage to spermatogenesis. No adverse effects from industrial exposure or clothing
Hypothermia	No adverse effects noted
Ionizing radiation	Dose-dependent effects at high but non'lethal doses. Reduce to "as low as reasonably achievable"
Noise	Conflicting results
Optical radiation (UV, visible, infrared, laser)	No adverse effect noted Subjective complaints with video displays
Radio-microwave radiation	No adverse effects in absence of non-thermal heating
Ultrasound	Same
Vibration	Little data

Table 10. Compilation of ascribed primary causes of infertility in three large U.S. reports (Verkauf 1983, Kliger 1984, Musich 1982). Estimation of how may couples at age 30 (infertility rate 10%) would be present with each ascribed cause and comments and assessment of possible preventive measures is made.

Category	%	Postulated # Preventions out of 1000 Couples	Comments	Likelihood of Acceptance
Ovulatory defects	27	27	The majority of ovulatory defects remain unexplained. Occurrences associated with medication, excess stress, athletic training, body habitus, and possibly substance abuse may be avoided and/or ameliorated.	Good, with education
Unexplained	21	21	Further basic and clinical research needed. Some episodes may be explained by more vigorous inquiry; smoking, substance abuse, training, body habitus, medications exposures, etc. Pregnancy at optimal ages for fecundity may preempt subsequent infecundity.	Good with further research and increased clinical diligence.
Male factors	19	19	Factors including STD infection, medications, substance abuse, smoking, surgery may be avoided and/or ameliorated. Surveillance for varicocele may be helpful.	Less likely, since fertility less of "male concern".
Tubal factors	19	19	PID and STD exposure may be avoided and/or reduced by modifications of sexual encounters, contraceptive use, surgical abortion. See factors under surgery. Periodic screening for STDs.	Good possibility that sexual expression can be made more "safe". Screening increasingly accepted "Home" STD screening kits will be popular.
Endometriosis	9	9	Use of oral contraceptives, avoidance of pelvic surgery during menses, and early childbearing in genetically predisposed individuals may prevent some instances.	Less likely since advice is complex and endometriosis is not perceived as threat by younger women.

Category	%	Postulated # Preventions out of 1000 Couples	Comments	Likelihood of Acceptance
Cervical factors	4	4	Limitation of and/or increased care during cervical manipulations. Increase recognition and treatment of cervicitis.	Good, with further health professional education.
Uterine factors	2	2	Limitation of and/or increased care during surgical uterine procedures. Use of appropriate chenoprophylaxis.	Good, with further health professional education.
Hyperprolactinemia syndromes	1	1	Recognize that medications (dopamine antagonists) may cause hyperprolactinemia.	Limited, due to small proportion of drug induced cases.
DES change	1	1	DES or similar substance should be avoided during pregnancy.	Should be complete
TOTAL*	103	103		
Prior pelvic**	21	21	Ovarian wedge resections and rupture of the appendix should be avoided. Careful tissue handling and precautions against adhesions mandatory. Screen for male and female genital tract cancers.	Good, with continued professional and public education

*Percentages add up to more than 100% because of combination of categories.
**Prior pelvic surgery was detailed in only one study (Muisch, 1982) Types of surgeries or surgical conditions inculded in order: ectopic pregnancy, ovarian wedge resection, ovarian cystectomy, ruptured appendix, drainage of pelvic infection, and cesarean section with infection.

Table 11. Primary prevention of infertility. An active, positive, assertive approach is optimal in preserving fertility. Comments apply to both males and females, except when gender differences are obvious or stated.

Comments	Problem
I. General	
1. Inadequate knowledge	Ensure that information on reproduction is available from parents, schools, clergy, and other sources.
2. Lack of perspective about reproduction	Learn about "family life" by example and in communication with parents and professions. Formulate "life plan" which includes career and reproduction plans.
II. Specific	
1. STDs and PID	A. Careful restrictions and consideration of possible sexual partners. Forthright inquiry and physical inspection for risks of STDs recommended.
	B. Preference for oral contraceptives for contraception and likely effect versus PID. Use condoms routinely with new sex partner.
	C. If sexually active, be periodically screened for STDs. STDs in both males and females are commonly asymptomatic.
	D. Recognize findings of STDs and seek medical care and ensure that correct treatment is given for yourself and partner, with follow-up.
2. Postpartum, postabortal, postoperative pelvic infections	Ensure that optimally safe birth and surgical services are available.
3. Exercise, nutrition, and stress	Recognize that regular strenuous exercise, rapid weight loss, low body fat composition, and stress can cause decreased fertility. Women are at higher risk than men.
4. Smoking, environmental exposure, drugs	Smoking, as well as other substance abuse, reduces reproductive potential and should be avoided. Environmental

	exposures are inadequately studied, but appear more common in males. Semen analysis can be performed.
5. Endometriosis	If strong family history for endometriosis, perfer oral contraception and specific possible endometriosis suppression. Oral contraceptives may suppress endometrisosis even in those not at high risk.
6. Cryptorchidism and varicocele	Undescended, especially intraabdominal testes should be treated as promptly as possible. Benefits of surveillence and treatment of varicocele unproven.
7. Chemotherapy and radiation	Risks of gonadal damage must be considered and if appropriate, gamete collection and/or oophoropexy should be performed.
8. Intercurrent illnesses	Many acute and chronic diseases cause anovulation and decreased spermatogenesis. Prevention of these effects is treatment of the primary disease.